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The American Heart Journal

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Original Communications

SOME CARDINAL CIRCULATORY SYNDROMES*

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NEW YORK, N. Y.

PRIOR to the final decade of the past century, slowing of blood flow was almost invariably attributed to cardiac weakness. Since then, studies on circulatory collapse in infectious diseases and traumatic shock have led to general recognition of the manifestations of circulatory failure initiated in the periphery. There have also been attempts, especially in France, to differentiate the clinical pictures characterizing failure of the individual ventricles and auricles of the heart. These teachings have not been widely adopted in this country, and many regard the distinctions as artificial.

In the following pages, the attempt will be made to demonstrate the feasibility and the utility of differentiating individual types of cardiac failure, each with a characteristic clinical picture resulting from a well-defined aberration in the dynamics of the circulation. Together with the failures of peripheral genesis, these constitute what we may term the *cardinal circulatory syndromes.* Preliminary to discussion of these cardinal circulatory syndromes, it may be well to describe briefly some of the means by which the heart accommodates itself to increased work.

To a large extent, the changes in the dynamics of the circulation in disease are merely exaggerations of the accomodative reactions in health.

DILATATION OF THE HEART

Older clinicians viewed dilatation of the heart as a passive process resulting from defective contractility or tonus of the myocardium. For several decades, however, the view has steadily gained ground that cardiac dilatation is a useful adaptation playing a fundamental part in the adjustment of the heart to increased work. Originally reached on purely clinical grounds, this conception has acquired a sound foundation through experimental investigations of physiologists on the dynamics of the heart.

*Read at the Graduate Fortnight of the New York Academy of Medicine, October 27, 1931.

These studies have shown that when either heightened arterial resistance or greater venous inflow increases the work of the heart, accommodation to the greater load involves increase in diastolic volume. Starling[1] found that when arterial resistance is increased, the heart fails to empty as completely during the first beats, so that the residual blood in the chamber at the end of systole is increased. Inasmuch as the venous inflow during diastole remains constant, the result is increased diastolic volume. However, as the diastolic volume mounts with successive beats, the output also rises until equilibrium is attained by output equalling inflow. There is a similar process of adaptation when the arterial resistance is constant but the venous inflow rises. In both cases, the adaptation to greater work accompanies larger diastolic volume of the heart, i.e., increase in the initial length of the muscle fibers. The mechanism by which this greater initial length of the muscle fiber causes it to contract more forcefully is in dispute. According to Starling,[1] it is the greater *length* of the fiber as such that causes it to free more energy when shortening, while Frank[2] and others believe that the heightened initial *tension* of the fiber is the coefficient that results in the more powerful systole.

Whichever of these views is correct, it is significant for the clinician that the adaptation of the heart to increased work involves at least diastolic dilatation. The compensatory significance of the dilatation of the appropriate chambers of the heart in arterial hypertension, valvular defects, etc., thus becomes clear.

From such compensatory dilatation, some investigators have endeavored to differentiate another variety, in which the elongation of the muscle fibers is a passive stretching. The conception is that although the work confronting the heart is not increased, the muscle gives way as a result of diminished contractility or tonus resulting from myocarditis, deficient blood supply, etc. This is the so-called myogenous dilatation. But even in such instances it would seem well to consider whether the dilatation is not to be viewed as compensatory. For it may well be that a functionally damaged heart muscle can meet a given load only by dilating as would a healthy myocardium under conditions demanding much more mechanical work. In other words, the diastolic volume of a chamber of the heart required to meet a given load varies inversely with the functional efficiency of the muscle.

HYPERTROPHY OF THE HEART

Dilatation is thus a compensatory process. It is, however, only the first line of defense of a chamber of the heart when called upon for increased work; after a longer or shorter time, dilatation is reinforced by hypertrophy. That dilatation precedes hypertrophy is obvious in the large majority of instances, and is probably always the case. This is well illustrated in acute glomerulonephritis with hypertension. In the

greater proportion of those who succumb in the first weeks, most often to acute failure of the left ventricle with pulmonary edema, the left ventricle is found dilated but not hypertrophied. On the other hand, when the duration of the disease is measured in months, hypertrophy is almost always present. Kindred observations have been made in experimental valvular lesions. The intimate association of hypertrophy with dilatation is well brought out by the observations of Kirch,[3] who found that both dilatation and hypertrophy are initated in the outflow tract of the ventricle with only subsequent involvement of the inflow tract. The recent detailed studies of Gross and Kugel (personal communication) have afforded results similar to those of Kirch.

What is the link that connects hypertrophy with antecedent dilatation? This is not entirely clear, but the utility of the process is elucidated by the following considerations: Inasmuch as the volume of a sphere is proportional to the cube of the radius, as a sphere increases in size equal increments in volume correspond to smaller and smaller increases in radius. In other words, the larger a cardiac chamber, the less its radius must be diminished to expel the same volume of blood. Thus the fibers of the dilated heart contract a shorter distance in maintaining the same stroke volume than do those of the normal organ. But the force of contraction must be correspondingly greater. *Dilatation thus leads to the necessity for a shorter but more powerful contraction of the muscle fibers, and hypertrophy would seem to be the adaptation to these altered conditions.* Of course, such a line of thought merely considers the wherefore and not the how of the process by which hypertrophy occurs in the dilated heart.

INCREASE IN RATE

In the majority of instances, though not invariably, the rate of the failing heart is increased. Within limits, acceleration of the heart fulfills a compensatory function. Henderson[4] found in the dog that the minute volume increases with the rate of the heart to about 120 beats per minute, is relatively constant between 120 and 240, and falls above the latter rate. The conditions for the development of a compensatory action by tachycardia are especially favorable in cardiac failure, for the shortening of diastole that accompanies tachycardia is neutralized to a large extent by the increased venous pressure, which accelerates diastolic filling. On the other hand, in auricular fibrillation the loss of the filling quota due to auricular systole militates against compensation by tachycardia. Similarly, the low venous pressure of patients in shock prevents tachycardia from notably increasing the output of the heart. The cases in which tachycardia is so rapid as to diminish the output of the heart will be discussed later.

The pathogenesis of tachycardia in cardiac weakness has not been entirely elucidated. It is not an intrinsic adaptation of the heart to

increased work, for Starling found in the heart-lung preparation that within wide limits increments in arterial resistance or venous inflow do not affect the rate. A factor that may be significant is the Bainbridge reflex. Bainbridge[5] found that increased pressure within the venae cavae close to the heart and the right auricle induces reflex acceleration in rate. It has also been found that similar tachycardia results from elevation of pressure within the pulmonary veins and left auricle. The increased pressure behind a failing chamber of the heart may thus initiate compensatory tachycardia. In those instances in which cardiac failure is accompanied by fall in arterial pressure, of which coronary occlusion is an outstanding example, reflexes initiated in the carotid sinus and aorta may also play a part in accelerating the heart.

THE CARDINAL CIRCULATORY SYNDROMES

In any attempt to analyze the clinical pictures of circulatory failure from the point of view of the underlying disturbances in the dynamics of the circulation, the primary and obvious distinction is between failure of cardiac and of peripheral origin. In the vast majority of instances, this differentiation is readily carried out at the bedside.

In the category of cardiac failure, further classification on a dynamic basis is often feasible. In certain cases, the cardiac failure is obviously a result of interference with diastole, either in consequence of mechanical incarceration of the heart or because of undue shortening of diastole in tachycardia. The term *diastolic insufficiency* may be used to designate such instances. Far more common is the cardiac insufficiency in which there is no hindrance to diastolic filling but in which contractility is inadequate. Such *systolic insufficiency* may involve the entire heart or may be confined to the right or the left ventricle, while the other chamber is functionally efficient—right or left ventricular failure.

It is doubtless also true that different mechanisms lead to circulatory insufficiency of peripheral origin, but as yet it scarcely seems feasible for the clinician to separate them. Common to these *peripheral insufficiencies* is stagnation of blood in one or another vascular territory so that the venous return to the heart is inadequate.

Tentatively, then, we may recognize the following cardinal circulatory syndromes:

1. Cardiac Insufficiencies:
    - A. Systolic insufficiencie—impaired contractility.
        - a. Failure of the left ventricle.
        - b. Failure of the right ventricle.
    - B. Diastolic insufficiencies—inadequate diastolic filling.
        - a. Mechanical incarceration of the heart.
        - b. Abbreviation of diastole by tachycardia.
2. Peripheral insufficiencies—deficient venous return to the heart.
3. Combinations of the above.

FAILURE OF THE LEFT VENTRICLE

Failure of the left ventricle occurs in the diseases in which the work of this chamber is increased or its muscle diseased. Hence, it is seen most often in arterial hypertension, disease of the aortic valve, and stenosis of the mouth or the trunk of the left coronary artery. Classical left ventricular failure may appear in acute glomerulonephritis, and is the chief danger in the first days of the disease. It also occurs in mitral disease with predominant regurgitation; when there is marked stenosis also, left ventricular insufficiency is unusual.

The clinical picture of isolated insufficiency of the left ventricle is characterized by symptoms and signs attributable to increased tension in the pulmonary circuit in the presence of normal pressure in the systemic veins.

The outstanding symptom is dyspnea. In almost every instance there is breathlessness on exertion. Often, however, the dominant type of dyspnea is paroxysmal, with especial tendency to occur at night, waking the patient in the first hours of his sleep—so-called cardiac asthma. In fact, the sole complaint may be of such nocturnal attacks of cardiac asthma. While questioning and examination almost always reveal that these patients are short of breath on climbing stairs or on other exertion, their way of life may be such that exertional dyspnea does not trouble them and that they suffer only from the nocturnal paroxysms. In the most severe of such attacks there may be acute pulmonary edema with its pink, frothy sputum. The pulmonary stasis often leads also to hemoptysis, usually only streaked sputum but occasionally copious.

Objectively, an interesting and important sign of the hypertension of the lesser circulation, as Moschcowitz[6] has termed it, is the accentuation of the second pulmonic sound. This is of especial significance in the presence of arterial hypertension. If the left heart of the hypertensive patient is adequate, the second sound is louder in the aortic than in the pulmonic area. But with failure of the left ventricle, the pulmonic second sound becomes accentuated. In such cases, I have often heard the second sound much louder in the pulmonic than in the aortic area despite a diastolic pressure of 120 mm. or higher. It is particularly significant when, in a patient with arterial hypertension whose aortic second sound has been the louder, the pulmonic second sound becomes the more intense under observation; this is excellent evidence of failure of the left ventricle. In acute glomerulonephritis, accentuation of the second sound in the pulmonic area, generally accompanied by gallop rhythm, warns of grave danger of left ventricular failure.

The negative feature characterizing isolated insufficiency of the left ventricle is the absence of engorgement of the systemic veins and liver. Measurement of the venous pressure reveals it within normal limits; I have often found the venous pressure but 5 or 8 cm. of water despite the presence of orthopnea. Since venous pressure is normal, edema is, of

course, absent. However, the patient may be cyanotic—usually a grayish cyanosis. In many cases the cyanosis is of pulmonary origin, for the warm hands show that the blood flow is not notably retarded. In other instances, to be sure, the cold extremities testify that slowing of blood flow also plays a part in the production of the cyanosis.

There is no constancy about the height of the arterial pressure. With severe coronary artery disease, particularly if there has been thrombosis of a large branch, previous hypertension may be reduced, even to below normal values. In other patients, despite severe orthopnea and other evidences of weakness of the left ventricle, the arterial pressure is maintained at a high level. During attacks of pulmonary edema, the pressure may rise strikingly, evidently a manifestation of the asphyxia.

It should be observed that the stage of isolated insufficiency of the left ventricle may last for years in patients with hypertension or coronary sclerosis, though more often signs of insufficiency of the right ventricle are soon superadded if the patient does not improve or succumb. I have seen isolated insufficiency of the left ventricle in severe form lasting over three years. In one patient at present under observation, it seems to have been present for eight years. In such cases, almost the only complaint is dyspnea, particularly paroxysmal nocturnal dyspnea. The patients are often afraid to go to sleep because of the nocturnal attacks. Not rarely, they are considered to suffer from bronchial asthma; I made this mistake recently. Sometimes, they go through repeated tests for hypersensitiveness. Some succumb to coronary thrombosis or other accidents while in the stage of isolated failure of the left ventricle, but more often the right heart sooner or later also gives way. It is an old observation that the dyspnea of such patients may be greatly relieved when the right heart fails, with swelling of the liver and feet; obviously, this is a result of the relief of the hypertension of the pulmonary circuit.

In mitral stenosis a disturbance in circulatory dynamics akin to that of left ventricular failure, and dominated entirely by the increased tension in the pulmonary circuit, may be present for years. The outstanding symptoms are exertional dyspnea and often recurrent blood spitting; but, contrary to left ventricular failure, nocturnal paroxysmal dyspnea is rare. As long as the right heart is adequate, increase of venous pressure and its consequences are absent. Such cases present the picture of *failure of the left auricle.*

FAILURE OF THE RIGHT VENTRICLE

The conditions in which failure of the right ventricle occurs are those which give rise to prolonged increase of tension in the pulmonary circuit, i.e., mitral disease, emphysema, various forms of pulmonary fibrosis, kyphoscoliosis, extensive pleural adhesions and effusions, the rare forms of disease of the pulmonary artery described by Ayerza, etc. Unusual

causes are organic changes in the pulmonary and tricuspid valves and disease of the right coronary artery. Most patients with left heart failure ultimately also develop insufficiency of the right ventricle, the manifestations of which then dominate the clinical picture. Such superimposition of right ventricular failure on insufficiency of the left heart often occurs under our eyes.

Failure of the right ventricle is, of course, manifested by engorgement of the systemic veins. In the vast majority of cases, this is documented by increase in venous pressure. I have, however, seen instances of this variety in which the venous pressure was not definitely abnormal, although the liver was enlarged and tender. But if the failure be not transitory, increase in venous pressure generally soon becomes demonstrable. In severe failure of the right heart, the venous pressure may rise to great heights; tensions well above 30 cm. of water are not uncommon. This rise in venous pressure, in addition to its deleterious consequences, may also fulfill a compensatory function. Since the energy unleashed by ventricular systole is proportional to diastolic filling, it is obvious that increased venous pressure with its resultant promotion of diastolic filling will tend to elevate the work done by the right heart. Moreover, increased venous pressure tends to accelerate the heart by the Bainbridge reflex. These two effects of increase in venous pressure are synergistic, for acceleration of the heart is effective in increasing output only if filling is accomplished with sufficient rapidity.

Palpable enlargement of the liver almost always accompanies the rise in venous pressure. The engorgement of the liver may also serve a compensatory function. It is generally believed that the increased abdominal tension during inspiration plays a part in the diastolic filling of the right heart, one factor being the squeezing out of the liver like a sponge. If the liver is engorged, the amount of blood thus squeezed out is presumably greater and so increases the diastolic filling of the right heart. The amount of blood that can be squeezed out of a congested liver is readily visualized by observing the swelling of the veins of the neck that accompanies manual compression of the acutely congested organ.

Cyanosis and dyspnea are almost always present. As a rule, however, in contradistinction to failure of the left ventricle, the cyanosis is relatively much more instense than the dyspnea. In fact, in many very severe instances of right heart failure with greatly increased venous pressure and extreme cyanosis, the patient does not volunteer dyspnea among his complaints and lies flat without any indication of orthopnea. The combination of engorged veins and deep cyanosis in the absence of striking dyspnea immediately suggests failure of the right heart.

In many instances, the cause of the disproportionately severe cyanosis is arterial anoxemia due to the pulmonary lesions primarily responsible for the strain on the right heart. But with severe failure the cyanosis

is not entirely pulmonary in origin; the cold extremities often indicate that slowing of the blood flow in the periphery with consequent increased reduction of oxyhemoglobin also plays a part. In addition, the polycythemia often present in these patients facilitates the appearance of cyanosis. A further factor has been emphasized by Uhlenbruck,[7] who has shown by experiments with inhalation of low concentrations of oxygen and high percentages of carbon dioxide that the irritability of the respiratory center in such patients with chronic arterial anoxemia is diminished. The condition of the patients is analogous in this respect to morphine intoxication, in which there is also deep cyanosis in the absence of dyspnea.

Another symptom of the more severe of these cases that has impressed clinicians is somnolence; I have seen stupor persist for days and weeks. This is presumably also a consequence of protracted oxygen want.

That edema and serous effusions may attain prodigious extent in these patients with high venous pressure need scarcely be mentioned.

I should like to refer briefly to the unusual instances of right ventricular failure resulting from disease of the right coronary artery. Such cases may run a chronic course with cyanosis, edema, serous effusions, and a large, hard liver, thus simulating Pick's disease. Dyspnea may be but slight and orthopnea absent. In a patient with this clinical picture who came to necropsy recently, paracentesis of the abdomen had been necessary four years before death and cardiac cirrhosis had developed. The picture of disease of the right coronary artery with acute failure of the right heart may be very striking. Such a case was recognized *intra vitam* by Dr. E. Libman by the concomitance of rapid and massive enlargement of the liver with the development of sino-auricular block.*

CARDIAC FAILURE DUE TO INADEQUATE DIASTOLIC FILLING

Interference with diastolic filling entails corresponding diminution in systolic output. Such inadequate diastolic filling may result from either limitation of diastolic relaxation or the abbreviation of diastole in excessive tachycardia.

The classical example of cardiac failure due to mechanical limitation of diastole is furnished by rapidly accumulating pericardial effusion. Cohnheim[10] long ago observed that when the pressure in the peri-

*The great significance of the venous pressure for the clinician has been repeatedly indicated in the foregoing. Nevertheless, measurements of venous pressure have not been widely applied in clinical work because of difficulties in carrying out the measurement. In a recent lecture, Lewis[8] has described in masterly fashion the rough estimation of the venous pressure by observation of the height of the blood column in the superficial veins of the neck. A very simple and apparently adequate method for the direct measurement of venous pressure has been introduced by Taylor, Thomas and Schleiter,[9] which I have found very useful. Using this method, the venous pressure in healthy individuals is between 4 and 8 cm. of water, rarely reaching 10 cm. Indications of the progress of patients with failure of the right heart can be obtained from the venous pressure. Thus, I have often seen successful digitalization in mitral stenosis with auricular fibrillation result within forty-eight hours in a fall in venous pressure from about 25 cm. of water to the normal level of about 6 cm.

cardial sac of a dog is raised by the injection of fluid, aortic pressure falls concomitantly with rise in venous pressure. Precisely the same phenomena are observed in copious pericardial effusion in man if it is formed with sufficient rapidity. That the mechanical limitation of diastole by the compressing fluid causes the cardiac failure is proved by the immediate relief that follows paracentesis. In a recent instance of purulent pericardial effusion with low arterial and high venous pressure, the physician taking the pulse could feel the hands become warmer as the pulse strengthened during the course of the paracentesis.

An analogous variety of cardiac failure resulting from limitation of diastole is encountered in thickening of the pericardium in which the contracting scar tissue incarcerates the heart, the Pick syndrome. Volhard[11] has described cases of this type in which the contraction of the thickened pericardium was so marked as to result in a small cardiac silhouette; when the heart was freed surgically, the patient improved. The syndrome has been reproduced experimentally by Beck,[12] who has shown in both animals and man that when the heart is freed from the incarcerating scar tissue which interferes with diastolic relaxation and may compromise the mouths of the venae cavae, venous pressure falls and cardiac output rises to normal.

The other type of cardiac failure due to inadequate diastolic filling results from shortening of diastole in tachycardia. The clearest example is the cardiac failure with rise in venous pressure and swelling of the liver that occurs in some episodes of paroxysmal tachycardia. Barcroft, Bock and Roughton[13] demonstrated in such a case that the minute volume was decreased during the attack.

The clinical picture of diastolic failure closely resembles that of insufficiency of the right ventricle, despite the fact that the filling of both ventricles is interfered with. The explanation is probably that the output of the right ventricle is so small that the left ventricle, despite equally severe functional impairment, is able to master it and thus avert the pulmonary engorgement which produces the characteristic symptoms of left ventricular failure. However, the diminution in output of the left ventricle may result in fainting and other manifestations attributable to cerebral anemia; these occur especially in the diastolic failure of paroxysmal tachycardia. In instances of copious pericardial effusion, features of both right and left ventricular insufficiency may be commingled. In such cases, the mechanical conditions may be such as to interfere relatively more with the filling of the left heart and thus result in pulmonary engorgement and agonizing dyspnea.

CIRCULATORY FAILURE OF PERIPHERAL ORIGIN

Since the capacity of the vascular tree is far greater than the volume of the blood, simultaneous relaxation of all the vessels would be incompatible with the maintenance of circulation. Variations in tonus of the

arterioles in different vascular territories guide the blood to the organs where it is needed. The capillaries also participate in the regulation of blood distribution; classical examples are the increase in the number of open capillaries in active muscle and the changes in the proportion of permeable glomerular loops as diuresis varies. Henderson,[14] Gollwitzer-Meier[15] and others have emphasized the importance of alterations in the capacity of the veins for the regulation of the circulation. This is of particular significance because the capacity of the venous side of the circulation is several times that of the arterial. The conception advocated by Hess[16] is that the arterioles serve to regulate the distribution of blood among the various organs while the veins are preponderant in regulating the total volume of the circulation. Diminution in the capacity of the veins immediately increases the return to the heart and therefore the output of that organ. Accessory factors of significance in aiding the venous return to the heart are contraction of the skeletal muscles and the respiratory movements; how strikingly muscular activity aids venous return to the heart is obvious when one asks a patient to clench his fist during venipuncture.

Evidently, a mechanism so elaborate as that regulating the distribution among the organs and the return to the heart of the blood must have a variegated pathology of its own. The classical example of such a circulatory disturbance originating in the periphery is surgical and traumatic shock. Peripheral factors are probably likewise dominant in the genesis of circulatory failure in many of the acute fevers, although in some of these, notably rheumatic fever and diphtheria, damage to the heart muscle plays a part or is predominant. The circulatory collapse that is now the chief danger in diabetic acidosis is also of this variety. Experimentally, circulatory failure of peripheral origin can be produced with histamine.

In each of these varied conditions, there appears to be stagnation of blood in the vascular periphery with resultant diminution in the venous return to the heart. That the pooling of blood in the periphery of the circulation is not due to cardiac weakness but is of peripheral genesis is proved by the low pressure in the large veins of the extremities. Even though the heart is functionally competent, the small return from the great veins entails an equally diminished cardiac output; hence the fall in arterial pressure, to which arteriolar dilatation may also contribute. The low arterial pressure in turn accelerates the heart through reflexes originating in the carotid sinus and aorta. The circulatory disturbance resulting from diminished venous return is one for which the heart cannot compensate. The reason for this is that filling is an entirely passive process on the part of the heart, which functions solely as a force pump, it does not, like a suction pump, aspirate blood from the venae cavae.

As to the causes of the stagnation of blood in the periphery, there are many theories but few established facts. The following mechanisms seem the best grounded:

1. It is widely held that the peripheral stasis is due to increased capacity of the small vessels, particularly in the splanchnic area, resulting from diminution in their tonus. Formerly, the stagnation was thought to be chiefly in the capillaries, but some recent investigators tend toward the view that most of the pooling of blood occurs in the very capacious venules. In the case of arteriolar relaxation, the actual increase in the capacity of the arterioles is probably not as significant as is what we may term the "guiding function" of the arterioles, i.e., the blood is no longer guided effectively to the active organs in which it is needed by the tonic contraction of the arterioles in the inactive parts.

2. Henderson[14] has for years defended the thesis that the peripheral stasis is due to diminished venous return to the heart—defective function of what he terms the venopressor mechanism—so that the blood stagnates in the venules. In Henderson's opinion, deficiency of carbon dioxide in the blood and tissues results in diminished tonus of the muscles and depresses respiration; when the venous return to the heart is deprived of these aids, peripheral stagnation is favored.

3. A number of investigators have found diminished circulating blood volume in peripheral circulatory failure. In some instances, such as diabetic coma or postoperative vomiting, this is at least partly due to concentration of the blood by dehydration. But in other cases the decrease in the volume of the circulating blood is believed to be caused by removal of blood from the rapid circulation into the various blood reservoirs, such as the spleen and the liver. This conception has been advanced especially by Eppinger.[17] It does not seem to me that the significance of the diminution in circulating blood volume associated with peripheral circulatory failure is as yet elucidated.

Considering the complexity of the mechanisms involved in the peripheral circulation, it would seem probable that there are various pathogenetically distinct types of peripheral circulatory failure, having in common stagnation of blood in one or another vascular territory and diminished venous return to the heart. But the means for differentiating these varieties are not yet at hand, and the clinician must be content with the separation of the circulatory failures of peripheral genesis from those due to cardiac weakness.

Before leaving the subject of peripheral circulatory failure, it would seem worthy of emphasis that both cardiac and peripheral failures may occur simultaneously. Thus, in cases of coronary thrombosis, the element of peripheral failure is often prominent and may completely dominate the clinical picture for a time. In such instances, although there is ashy cyanosis and the extremities are cold, I have repeatedly

found the venous pressure to be low. Despite a large infarct in the left ventricle, there may be no evidence of pulmonary congestion for a considerable time; the pulmonic second sound is not accentuated and the patient lies flat on his back without orthopnea. Evidently, so much blood is pooled in the periphery that the venous return is small enough to be within the capabilities, for a time at least, of even the severely damaged heart. Possibly, such cases are to be included in the concept of traumatic shock, the infarction of the myocardium being the responsible trauma. But the possibility must also be weighed whether the peripheral pooling of the blood is not a protective measure—effected through as yet unknown mechanisms—to relieve the acutely damaged heart.

Therapeutic considerations have not been broached in the foregoing discussion. That the treatment of circulatory failure of peripheral origin differs fundamentally from that of cardiac failure is, of course, well known. But I believe it has not been adequately emphasized that the therapeutics of the various types of cardiac failure must be individualized in accord with the nature of the disturbance in the dynamics of the circulation. Time will permit only one illustration of the importance of such therapeutic individualization: The sovereign domain of digitalis is failure of the right heart; I have convinced myself by protracted observation that it is rarely efficacious in isolated insufficiency of the left heart or in diastolic insufficiency. That is, it has not seemed to me that the results obtained by digitalization in isolated failure of the left ventricle by digitalization are superior to those observed by bed rest, fluid and salt restriction, and perhaps the administration of salyrgan without the additional use of digitalis. The difference is not entirely explained by the fact that auricular fibrillation occurs predominately with right heart failure, for there may be excellent therapeutic response to digitalization in this type of failure with regular rhythm. Whatever the explanation may be, much unnecessary digitalization will be avoided by realization that the sphere of usefulness *par excellence* of digitalis is insufficiency of the right heart, and that when the drug fails in other varieties of cardiac insufficiency, the only effect of increasing the dose is liable to be intoxication. The relation of the type of cardiac failure to the therapeutic response would seem worthy of more study than has hitherto been accorded it.

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CLINICAL ASPECTS OF ARTERIOSCLEROSIS*

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THIS discussion of human arteriosclerosis is undertaken with a certain unwillingness, because as every student of the subject must appreciate, our ignorance of this very common affection far overshadows our knowledge. A search of past writings for established fact leads to disappointment; hypotheses there are in abundance, but these frequently express opposite views concerning the cause and nature of arteriosclerosis.

For the purpose of this discussion I exclude those changes in the arteries due to syphilis, tuberculosis, trauma, toxic agents leading to thrombosis, and that rather rare inflammatory process, periarteritis nodosa. With less justification perhaps I exclude also the medial necrosis and calcification of peripheral vessels, described by Mönckeberg. I shall use the older and better known term "arteriosclerosis" introduced by Lobstein to denote that most common affection of the arterial system, of undetermined etiology, rarely absent in advanced life, and characterized by a thickening of the intima accompanied by the deposition of fat. Changes in the media are usually mild, although in some instances they are marked. Later sclerosis and calcification occur, which give to the arteriosclerotic artery its most characteristic appearance.

To enter upon a discussion here of the anatomical changes in arteriosclerosis would carry us far afield and would be productive of nothing new. Whether the process is primarily in the intima or in the media, or whether it is inflammatory or degenerative in nature is not settled. Klotz[1] thinks that the sclerotic changes in the vessels are due for the most part to intimal disease caused by infectious processes, work and old age, while MacCallum[2] has stated that the media in the aorta and visceral arteries seems relatively little changed in comparison to the extent of the intimal alterations. Included here are those changes in the smaller ramifications of the vascular tree known as arteriolar sclerosis. No attempt is made to differentiate this process from arterial sclerosis because the two are very frequently associated, and so far as we now know they may have a common pathogenesis.

Arteriolar sclerosis affecting arterioles of the order of the vasa afferentia in the kidneys is characterized by the irregular deposition of hyalin under the endothelium as seen best in longitudinal sections of

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the arteriole. Such hyalinized areas may undergo a fatty change which can be demonstrated by lipoid stains such as sudan III. As the process advances the lumen of the vessel is narrowed or completely obliterated. In larger arterioles one sees only the hyperplastic type of intimal thickening with retrogressive and fatty changes and later proliferation of connective tissue. Often in advanced cases the media shows degenerative changes with complete replacement fibrosis. Medial hypertrophy of the kidney arterioles is seen particularly in individuals under forty dying of hypertension.

Reviewing the present day conceptions of the etiology and pathogenesis of arteriosclerosis, one finds much speculation and many hypotheses often masking as fact. In a review of the subject in 1922, MacCallum[2] stated: "Arteriosclerosis is one of those diseases difficult to explain because it develops so slowly through long years of life, during which a great many possible causes have had an opportunity to affect the tissues. Hence every conceivable idea has been expressed or tenaciously maintained regarding the condition and many of them are so vague and ill supported that it is wearisome to discuss them. None, however, is clearly demonstrated to have a definite bearing on the etiology of arteriosclerosis and we are quite as ignorant of its underlying causes as were our fathers in the days of Morgagni."

Aware of the truth expressed in this quotation of MacCallum, we find it difficult, however, to dismiss summarily from consideration certain factors which have long been thought to be of some significance in the cause of human arteriosclerosis. I refer to the influences of heredity, to the ravages of the ageing process, to hypertension, and to those changes in our environment incident to our civilization, not because these are in any sense all the factors that may be involved, but the evidence in their favor is perhaps open to less criticism than that presented by other alleged etiological agents.

INCIDENCE OF ARTERIOSCLEROSIS

Accurate data on the present incidence of arteriosclerosis are not available, but indirectly, certain more or less pertinent facts are obtained by a study of mortality and morbidity statistics. These show for the registration area in America, first, that heart disease is the leading cause of death at present and, second, that the mounting incidence of heart disease during the past two decades occurs in individuals past forty years of age. For example, heart disease in the state of New York, excluding New York City, has been the leading cause of death since 1912 with the exception of the year 1918 when pneumonia held first place. The curves show an almost continuous rise from a rate of 133.5 in 1900 to 279.9 in 1928, when 50.6 per cent of the deaths were between the ages of forty and seventy, and only 8.3 per cent of deaths from heart disease were under forty years of age.

Assuming a certain error inherent in such data, there is little reason to doubt the statement that the most significant factors in heart disease beyond forty are vascular decay, coronary arteriosclerosis, and those changes in the smaller arterioles that we know are so frequently associated with hypertension. If, in addition, we add that group of individuals beyond forty who die of cerebral arteriosclerosis (thrombosis or hemorrhage) and those dying of renal insufficiency secondary to vascular disease, it is apparent that at the present time the expectancy of life of the majority of people beyond middle age is determined by the state of the arteries. Long ago it was said "A man is as old as his arteries." This truth is even more apparent today than ever before.

Much attention is given in some quarters to the steadily mounting morbidity and mortality rates from cardiovascular disease, and a variety of opinions is expressed concerning their significance; but before any definite conclusions are reached, it is necessary to know much more than we do at present concerning many factors that appear to influence the incidence of arteriosclerotic changes in vessels.

Data on the life span show that there are today in this country more people fifty years of age than ever before. Only a few decades ago the age at which most people died was 45; now it is 60. The control of some of the important causes of death in infancy and childhood has increased the number of people past middle life—in the arteriosclerotic age—hence a certain natural increment in the incidence of vascular disease is to be anticipated. Furthermore, modern hygiene and preventive medicine are striving daily to increase the number of individuals (both fit and unfit) that mature to approach the involutionary period of senescence. Man is exercising more and more control over his environment, and there are those who point with pride to his accomplishments in prolonging human life, but the biologist and the eugenist ponder the ultimate results of our present day methods as applied to the human race. They see the waning influence of natural selection and wonder if we can continue to thwart nature without paying the penalty in quality if not ultimately in quantity. In fact, there is some reason to believe that nature is already exacting her toll. Professor Forsyth[3] of Dartmouth has presented evidence to show that the length of life in this country is actually decreasing. From a critical analysis of mortality statistics he concludes that the American adult today cannot expect to live as long as his father or grandfather. There is little question that many individuals today are maturing to propagate the race who would not have survived in the more rigorous environment of our forefathers. If the wearing quality of our arteries is in any way determined by our heredity (a point emphasized by the late Dr. Osler), may we not expect an increasing number of people whose vessels may wear reasonably well for the earlier decades of life but as age comes on the shoddy appears in the form of early deterio-

ration of the vascular system. It appears that this view, admittedly difficult either to prove or disprove, cannot in the light of our present knowledge be summarily dismissed as sheer speculation.

CLINICAL ASPECTS OF ARTERIOSCLEROSIS

Although we are far from a solution of the problem of the pathogenesis of human arteriosclerosis, valuable contributions to our knowledge have been made by both pathologists and clinicians in the days since Bright. Time will not permit a discussion of the voluminous literature that has grown up on the subject in the past century, but it is necessary to mention the contributions of a few workers who have been most responsible for our present day conceptions. These are not perfect and they are slowly changing, but there is little doubt that the informed clinician at present is much better equipped than were his predecessors of the past generation to appreciate the variety of clinical conditions either associated with or directly due to arteriosclerotic changes in the vascular tree.

Knowing as we now do the frequent association of hypertension and left ventricular hypertrophy with sclerotic changes in the intimate vasculature of several organs—most often the kidneys—it is not surprising that the early students of kidney disease should have been concerned also with the problem of vascular disease. Bright[4] observed the occurrence of thickened vessels and cardiac hypertrophy in patients with contracted kidneys, but he had no clear conception of the causal relation. To understand the origin of the term "Bright's disease" and "Bright's kidneys" and to appreciate the influence that these terms have had on moulding our views even to the present time, we should recall that Bright's work dealt with no particular form of renal disease but included all cases with an albuminous urine during life and a scarred kidney postmortem. Kidney lesions were no further classified by Bright than as "large and smooth" and "small and granular," exceptions being regarded as intermediate stages in the process of development from the large to the small kidney. Originally, therefore, the term Bright's kidney included many forms of renal disease. It is interesting to note that following Bright's work and persisting for many years were certain conceptions regarding kidney disease which have done more to retard than to advance our knowledge. Chief of these were: First, that all types of scarred kidneys were manifestations of one disease process at different stages; and, second, that the associated lesions of other organs, such as those of the heart and arteries, were the effects of renal disease and due to progressive renal insufficiency.

It was not until some twenty years after Bright that the vascular lesions associated with renal disease received much attention. In 1852 Johnson[5] showed that in one form of chronic Bright's disease the

smaller arteries not alone in the kidneys but also in other viscera were thickened—changes which he ascribed to antecedent renal disease. The contribution which marked an epoch in our knowledge of vascular disease was that of Gull and Sutton[6] in 1872. They confirmed Johnson's observations but took an important step forward by showing that a diffuse vascular disease of the smaller vessels (arteriocapillary fibrosis) may occur without serious renal damage. They further suggested that left ventricular hypertrophy was due to the change in the minute arteries and capillaries and not to renal insufficiency. The observations and deductions of Gull and Sutton are all the more remarkable when we recall that they were made with imperfect histological methods and with no knowledge of clinical blood pressure. As conclusive as their work appeared, it was not a death blow to the older conceptions of the dependence of cardiac hypertrophy and arteriosclerosis upon renal disease.

About twenty years after the work of Gull and Sutton, the sphygmomanometer was introduced into clinical medicine by von Basch. As clinical data on blood pressure gradually accumulated, it was but natural that some association between abnormal elevations in blood pressure and sclerotic changes in vessels should be postulated, and supporting evidence for this view was afforded by those incidences of hypertension associated with demonstrable sclerosis of the accessible arteries. However, exceptions to the rule were not long in appearing. Von Basch in 1893,[7] after observing many cases of hypertension without demonstrable arterial changes, concluded that the hypertension was but a precursor of arteriosclerosis, and to designate such conditions he used the term "latent arteriosclerosis." Still lurking in the background now more than twenty years after Gull and Sutton's work, and more or less dominating the clinical thought of the time was the old teaching concerning the unity of arteriosclerosis and kidney disease. To bring the earlier observations on blood pressure into line with this view, it was taught that hypertension was a manifestation of arterial change which in turn resulted from renal disease. Therefore individuals with an abnormal elevation in blood pressure were regarded as having, or destined to develop Bright's disease and renal insufficiency. Such was the generally accepted and almost universally taught hypothesis concerning the relationship between arteriosclerosis, blood pressure, and kidney disease, in the early 90's of the last century.

In retrospect we may say that the stage was set for recognition of that large group of individuals with chronic hypertension who never develop renal insufficiency, and who have no significant changes in the palpable arteries. For this step forward we are indebted to Allbutt, although about the same time Huchard[8] in France was aware of the frequency of nonrenal hypertension. Long and careful observations on

patients led Allbutt[9] to the following well known classification: (1) hyperpiesia—individuals with chronic hypertension with little or no renal involvement who die of heart failure or apoplexy; (2) renal disease with or without hypertension; (3) decrescent arteriosclerosis, primarily of the larger arteries, not necessarily accompanied by hypertension. In his zeal to stress the importance of hyperpiesia and to have it regarded as a distinct malady, Allbutt failed to recognize, or at all events did not include in his classification, those cases of primary hypertension that die of renal insufficiency. Such cases have until very recently presented a barrier to any classification of nephritis; they have led to no little confusion between clinicians and pathologists and have helped to keep alive the old conceptions of the renal origin of hypertension.

After Gull and Sutton, the most outstanding contribution from the pathological standpoint was made by Jores[10] in 1904, who showed for the first time that the scarred kidney, formerly regarded as the seat of chronic interstitial nephritis, was in reality due to arteriosclerosis of the smaller renal vessels. He further observed[11] that patients with atrophic granular kidneys had hypertrophied left ventricles, and more often died of cardiac failure or apoplexy. Jores' work supported that of Allbutt and served to emphasize the view that cardiac hypertrophy and hypertension were not due to renal involvement. Opponents on the other hand supported their argument by citing cases of hypertension that died of uremia. For several years following the work of Allbutt and Jores clinicians generally, recognized that some relationship existed between arteriosclerosis, hypertension, cardiac hypertrophy and granular kidneys, but, as most of us recall, the teaching of twenty years ago was anything but clarifying. The diagnosis of cardiovascular renal disease was commonly made, but so far as the student was concerned, just what part of the clinical picture was due to cardiac failure and what to renal insufficiency was seldom determined with any degree of accuracy. Retained body fluid and an albuminous urine were usually sufficient evidence to incriminate the kidneys.

The clear recognition of two types of primary hypertension, one with renal insufficiency, the other without, and the corresponding vascular renal lesions were established by Volhard and Fahr[12] in 1914. Thus for the first time the hitherto puzzling case of hypertension and renal insufficiency was brought into line, but not without an argument among pathologists which has continued to the present time. This arose from the assumption by Volhard and Fahr that the kidney lesions, particularly in the glomeruli, in their cases of so-called malignant hypertension dying of renal insufficiency, were not due solely to vascular damage but were a combination of vessel and inflammatory renal changes, their Kombinations—Form. Both authors have now changed their original views, Volhard[13] holding that the vascular renal

lesions are ischemic in nature, the result of vascular spasm. This phase of the subject is presented in a recent contribution of Klemperer and Otani,[14] who distinguished two types of vascular lesions, one a rapidly progressive atherosclerosis, the other, an inflammatory lesion superimposed on an antecedent arteriosclerosis.

The above brief resume of a few of the more important contributions since Bright, gives us a glimpse of the development of our present knowledge concerning the relationship of arteriosclerosis, hypertension and certain forms of kidney disease, and it also indicates the difficulties encountered in the past in correlating clinical and pathological observations. That our present knowledge is immature is apparent to all, but may not its abundant heritage promise much for the future?

Before attempting what we may call a pathological-physiological classification of arteriosclerosis, certain well known facts may be emphasized: First, that those changes in the arterial tree that we call arteriosclerosis are most capricious in their distribution, appearing in the greater circulation from the sinus of Valsalva to the smallest arterioles (for some reason not known at present the arteries of the lesser circulation in most cases are singularly spared). The process may be generalized in some instances and sharply localized in others. Second, that the functional significance of arteriosclerosis varies greatly; often there is no parallelism between the extent of the process and the associated functional disturbances. For instance, we see extensive changes in the larger arteries that offer no barrier to longevity, and on the other hand, the process may be confined to a few millimeters of the coronary artery and cause sudden death in the prime of life. Serious damage to the intimate vasculature of the kidney is found in young people dying of uremia. Chronic hypertension and sanguineous apoplexy usually are associated with damaged cerebral vessels. Many other examples might be cited to illustrate the variety of clinical pictures associated more or less intimately with vascular disease. Our limited knowledge at present precludes a satisfactory classification of arteriosclerosis (this term to include both large and small vessel involvement), but since we as clinicians are primarily concerned in correlating the clinical and pathological findings, the following scheme may serve as an outline in approaching a discussion of the subject.

This outline makes no claim to perfection and it has many vulnerable spots. To perceive them is to appreciate the difficulties in associating functional disorders and anatomical changes, particularly changes so irregular in distribution as are those of arteriosclerosis. Certain quite obvious objections may be made to the association of arterial and arteriolar sclerosis and blood pressure, but in indicating a relationship between hypertension, for example, and small vessel disease, no more is implied than the fact that most individuals with so-called essential hypertension show at post-mortem examination more or less marked

TABLE I

PATHOLOGICAL PHYSIOLOGY OF ARTERIOSCLEROSIS

ARTERIOSCLEROSIS (LARGE ARTERIES) WITHOUT HYPERTENSION			ARTERIOLOSCLEROSIS (ARTERIOLES) WITH HYPERTENSION AND CARDIAC HYPERTROPHY OFTEN COMBINED WITH LARGE VESSEL SCLEROSIS			
(1) Coronary arteries	Stenosis (ischemia)	Angina pectoris	(5) Heart	Dilatation		Myocardial insufficiency
	Thrombosis	Myocardial insufficiency		Coronary disease as in (1)		Angina pectoris
(2) Cerebral arteries	Stenosis (ischemia)	Mental deterioration	(6) Brain	Vascular changes as in (2)		Mental deterioration
	Thrombosis	Apoplexy				Apoplexy
	Rupture	Paralysis				Paralysis
(3) Renal arteries	Ischemic necrosis	Scarred kidney—(very rarely insufficient)	(7) Kidney	Vessel sclerosis with or without arteriolar necrosis	Often granular atrophy	Uremia in approximately 10 per cent
	Infarction					
(4) Aorta	Inelasticity with or without dilatation	Peripheral circulatory disturbances				
	Rupture					
	Calcification of aortic valves (stenosis)	Myocardial insufficiency				

lesions of the arterioles. We have no proof that the arteriolar lesions are the cause or the result of hypertension, and no such implication is intended in this outline. As a matter of fact there are authorities who uphold either view. Lesions of the arterioles are found in the order of frequency and severity in the kidney, spleen, pancreas, liver, brain, adrenals and gastrointestinal tract. Keith and his associates[15] at the Mayo Clinic recently have published observations on the arteriolar lesions in the skeletal muscles in cases of hypertension. This work seems promising but more data are necessary before definite conclusions can be drawn.

The occurrence of large vessel sclerosis without hypertension as shown here is also open to criticism because of the frequent involvement of the arteries as well as the arterioles in individuals with hypertension. On the other hand, one finds it necessary to include that large group of elderly people who have outspoken arteriosclerosis of the large arteries with no undue elevation in blood pressure. Certain it is that there is not the obligate connection between large vessel sclerosis and hypertension that we know exists between small vessel disease and hypertension. For this reason there appears some justification for indicating the relationship as shown here. The right side of the diagram in Table I showing items 5, 6, and 7 under "small arteries" and in relation to hypertension is a functional grouping emphasizing a fact well established at present, namely, that the cause of death in individuals with primary or essential hypertension is in the order of frequency: heart failure, a cerebral accident and renal insufficiency. In a series of 400 autopsied cases of essential hypertension, Bell and Clawson[16] found myocardial insufficiency including coronary disease, responsible for 60 per cent of the deaths. In a similar series of 100 autopsied cases at the Cleveland City Hospital we found as the cause of death myocardial failure in 68 per cent, cerebral accident in 22 per cent, and renal insufficiency in 10 per cent. Allowing for certain errors inherent in such data, they show that the most common contingency in essential hypertension is heart failure, and by all odds the least is renal insufficiency. These facts are not so widely appreciated as their significance merits. The old conception of the renal origin of hypertension still survives to influence diagnosis and the therapeutic management of patients. Red meat is still prohibited and a failing heart is neglected because an albuminous urine is regarded as Bright's disease rather than as chronic passive congestion.

The appearance of coronary arteriosclerosis in two positions in this diagram illustrates again the difficulty in correlating anatomical changes and functional disorders. Anatomically, the coronaries are large arteries, and from a functional standpoint coronary sclerosis occurs in patients without hypertension, but it also is associated frequently with small vessel disease and hypertension. Indeed, more or less coronary arteriosclerosis is almost always found in hypertensive heart failure,

so that, in a scheme such as this, it must appear on the one hand associated with hypertension, and on the other hand without hypertension. For the same reason, we must include cerebral arteriosclerosis under the two headings. The arrangement in 5 under "small arteries" is made to indicate, first, that coronary arteriosclerosis frequently occurs and is often an important factor in hypertensive heart failure, and, second, that as a result of coronary disease the clinical picture in hypertension may be that of Heberden's angina pectoris or coronary thrombosis. In 6 we see the second most common cause of death in hypertension—a cerebral accident due to a ruptured cerebral artery or to thrombosis of a sclerotic vessel. Under 7 we include that group (approximately 10 per cent) of the cases of hypertension that die of renal insufficiency. Here we may distinguish two general types, one of long standing hypertension—a slowly progressive vascular lesion in the kidney with renal atrophy and ultimate insufficiency—the other a more rapidly developing vascular lesion, usually in young individuals, with little or no renal atrophy, and death in uremia. In group 7 are included those instances of granular atrophy of the kidney secondary to vascular lesions, so commonly found at autopsy in hypertensive patients. Such forms of renal scarring which up to a few years ago were called chronic interstitial nephritis, we now know, seldom lead to renal insufficiency. In other words, from 85 to 90 per cent of patients with essential hypertension and arteriolar sclerosis die of heart failure or a cerebral accident before the vascular lesion in the kidney progresses to the point of renal insufficiency.

The left half of this outline is made to include those instances, usually in elderly people, of widespread and often extensive changes in the larger arteries without hypertension. Here reference is made to four large arterial systems, because the functional disturbances associated with changes in these vessels often lead to fairly distinct clinical pictures, the exception being the renal arteries shown in group 3. For example, coronary arteriosclerosis is seen as the anatomical basis for certain cases of myocardial fibrosis and functional insufficiency, for instances of angina pectoris and coronary thrombosis in patients who have never had hypertension. Also the mental deterioration in encephalomalacia from cerebral arteriosclerosis is well known, as are also the apoplectic stroke and paralysis.

The kidney is so often scarred in arteriosclerosis of the larger arteries that we include it under group 3. Changes in the larger vessels of the kidney often lead to occlusions with atrophy of kidney substance. This causes the irregular pitting so often seen in the senile kidney. Such changes, however, seldom cause atrophy of sufficient kidney parenchyma to lead to functional insufficiency.

Sclerosis of the aorta may be extreme and yet cause no symptoms. However, as the vessel approximates rigidity the pulse is more rapidly

propagated to the periphery, as shown by Bramwell.[17] More of the shock of ventricular systole is transmitted peripherally, and we find an abnormal excursion of the vessels from the aortic arch, for example the carotids. Sclerotic changes at the root of the aorta not infrequently involve the valve cusps, which become rigid, are unable to approximate the aortic wall during systole, and may lead to a high grade of aortic stenosis and death from heart failure. Incidences of aortic insufficiency ascribed to arteriosclerosis are often due to syphilis which may not be recognized grossly in the presence of advanced arteriosclerosis. Mention here may be made of an interesting anatomical finding first called to my attention by Professor Erdheim. He points out that the first few centimeters of the aorta are singularly spared in individuals who attain seventy years or more, although the remainder of the vessel is more or less extensively diseased. On the other hand, marked involvement of the first 3 to 4 centimeters appears to be incompatible with the proverbial three score and ten years. Exceptions to this rule are very rare. In searching for some explanation of this fact, one is reminded of the evidence indicating that the first part of the aorta is nourished from the coronary arteries, so that it is possible some relationship between coronary disease, at least of those branches that supply the aortic root, and sclerosis in this region exists. This matter merits further study.

The reference to combined lesions, as indicated in the right half of this diagram, is of course absolutely necessary, since several combinations of functional and anatomical changes may occur. For example, the larger arteries are almost always involved in long standing cases of hypertension and, indeed, the clinical course may be dominated entirely by the large vessel disease.

At this point I desire to present briefly the salient clinical and pathological findings in one case which illustrates the extent of the problem of vascular disease. Those of you who attended the Cleveland meeting of the American College of Physicians in 1927, will recall a boy aged twelve years whom I demonstrated as an example of juvenile nonrenal hypertension.

This boy developed normally, and except for an attack of lobar pneumonia at the age of eight years, he was in good health until eleven years of age. There was no history of rheumatic infection or scarlet fever. One year before coming under our observation he noticed undue breathlessness and palpitation while at play. He complained also during this year of rather regularly recurring attacks of severe headache. These symptoms progressed and formed the chief complaint on admission to the hospital, January 20, 1927.

Physical examination revealed a well-developed and alert boy of good color, in no distress, and with no puffiness about the face or edema elsewhere. Blindfolded, one would have said from palpation, that the accessible arteries were those of an old man. They were thickened and tortuous, and it was apparent that the blood pressure was elevated, and when measured it was found to be 280 mm. of mercury systolic, and 175 diastolic. At a glance one was impressed by the vigor and position of the

cardiac impulse, which was maximum in the sixth left intercostal space, extending almost to the anterior axillary line. At the apex the heart sounds were loud and booming, but as one approached the base a loud diastolic murmur was audible, with maximum intensity over the manubrium. In this position one also heard a snappy and tympanitic second sound followed at once by the blowing diastolic murmur. It was thought that this murmur was due to relative incompetence of the aortic valves, as it entirely disappeared when the systolic blood pressure was lowered from 280 to 190 by the administration of nitroglycerine. It is of note also that this acute drop in blood pressure always caused a severe headache.

The eyegrounds were typical of hypertensive retinitis. Neither disc was discernible from swelling of the adjacent retina. There were numerous areas of recent hemorrhage and a few whitish spots were observed. Only a few retinal arterioles were visible. These showed marked sclerosis. Further clinical study of the case revealed a normal blood picture, hemoglobin 90 per cent with 4.3 million red blood cells per cubic millimeter. The blood urea nitrogen on several occasions varied between 40 and 60 mg. per 100 c.c. The urine was pale and the specific gravity varied between 1.010 and 1.015. It always contained albumin and the sediment showed a few casts. The phthalein output was 50 per cent in two hours.

During the first month in the hospital, the symptoms complained of on admission improved, and the child appeared so well that his parents insisted upon taking him home. Two weeks later, and while at home, he developed suddenly a right-sided hemiplegia with the signs of an upper neurone lesion of the seventh nerve. Two days afterwards he was readmitted to the hospital, but no improvement in his condition occurred. His paralysis continued, he became more and more lethargic, and died April 5, two and a half months after his first admission. The anatomical diagnosis was as follows: marked generalized arteriosclerosis; arterial and arteriolar sclerosis of kidneys; cardiac hypertrophy (weight 475 grams); massive cerebral hemorrhage, left; hemorrhagic infarcts of intestines; acute splenic hyperplasia; edema of lungs. Microscopically arteriolar lesions were demonstrated in the kidneys, liver, spleen and pancreas. For the following histological description of the kidney lesions I am indebted to my colleague Dr. Harry Goldblatt. One of the striking features is the relative absence of glomerular lesions. An occasional glomerulus shows fatty degeneration or focal hyalinization of the tuft, with or without adhesion to the capsule. The most striking pathological change affects the blood vessels and especially the interlobular and afferent vessels. In the larger arterioles there is mainly thickening of the intima due to cellular proliferation. In the smallest ones the thickened, proliferated intima shows patchy or complete hyalinization with or without fatty degeneration; which shows well in sections stained with sudan III. The media of the smaller vessels is definitely hypertrophic but in most instances shows no other pathological change. The vascular lumen is in all instances reduced in size and in many of the vessels it is completely obliterated.

From the above account we see a case of extensive and severe diffuse vascular disease with hypertension and death from cerebral hemorrhage, in a boy of twelve years. Certainly we cannot invoke the ageing process, and there is little evidence that infection played an etiological rôle in the production of the vessel disease in this case.

In summary, we may say that the present day clinician sees in human arteriosclerosis a pathological process affecting the arterial system of the greater circulation from the largest to the smallest vessels, usually insidious in its onset, and most irregular in its distribution. Its pathogenesis is an unsolved problem, but in speculating we turn to

the influence of such factors as heredity, the ravages of age, hypertension, and those changes in our environment incident to modern civilization. When we know more about the causes of essential hypertension, we shall be farther on the road to the solution of the problem of arteriosclerosis, particularly the form that involves the smallest vessels, the arterioles.

We have seen that statistics indicate a mounting incidence of vascular decay, particularly in middle life, but we are reminded of the fact that individuals are living longer today than ever before, and deterioration of the arteries appears to be a favorite method of Nature to eliminate us after our biological responsibilities have been fulfilled. Complicating the problem and exerting an influence difficult to evaluate, are our present day efforts to thwart the law of natural selection.

One is reminded of the proverb, "So long as more remains to be done, nothing seems done." However, the canvas is being painted, a high light here, a shadow there, and if we are at present forced to speculate on the appearance of the final picture, we should be stimulated rather than deterred in our efforts to solve one of the most important and most perplexing problems with which the clinician and pathologist have to deal—the problem of vascular disease.

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THE ORDER OF VENTRICULAR EXCITATION IN HUMAN BUNDLE-BRANCH BLOCK*†

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IN previous articles from this laboratory[1, 2] it has been pointed out that, in accordance with the laws which govern the flow of electric currents in volume conductors, the potential variations produced by the cardiac muscle are very much greater in magnitude in the immediate neighborhood of the heart than at a distance from it. It has been shown that when one electrode of the string galvanometer is placed upon the precordium, the position of the second electrode, so long as it is distant from the heart, has comparatively little influence upon the form of the ventricular electrocardiogram. Attention has been called to certain resemblances between leads of this type‡ and direct leads of the kind employed by Lewis and Rothschild[3] in which one electrode is placed in actual contact with the ventricular muscle and the other upon the chest wall. In both cases the form of the ventricular complex is determined in a very large measure, although not to quite the same extent in the former as in the latter, by the potential variations of the exploring electrode; in both cases the muscle units which lie nearest this electrode exert individually a much greater effect upon its potential than those which are more distant from it.

Curves obtained by leading from points on or near the heart to one of the extremities utilized in taking the three standard indirect leads may be freed from the influence exerted by potential variations of the indifferent electrode by a method which we have recently described.[4] When this electrode is placed upon the left leg the correction is made by subtracting from each ordinate of the recorded curve one-third of the sum of the deflections, measured in millivolts, inscribed in Leads II and II at the corresponding instant in the cardiac cycle. It is possible in this way to determine, at least approximately, the time course of the potential of the exploring electrode, and thus to eliminate any difference beween direct and semidirect leads for which potential variations of the indifferent electrode are responsible.

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†A brief preliminary report of the observations upon which this article is based appeared in the *Proc. Soc. Exper. Biol. and Med.* **27**: 586, 1930.

‡We term all indirect leads in which one electrode is placed very much closer to the heart than the other *semidirect leads*. We call the electrode which is nearer the heart the *exploring electrode*; that which is more distant, the *indifferent electrode*. We refer to semidirect leads in which the exploring electrode is placed upon the precordium as *precordial leads*.

So far as we are aware, there is no reason to believe that in direct leads of the type under consideration the exploring electrode bears any special relation to the ventricular muscle other than that of great nearness to the fibers lying just beneath it. In direct leads from the outside of the exposed heart, it is true that the exploring electrode is in contact with a surface which, if we neglect the thin epicardium and film of fluid which covers it, is bounded by a di-electric, but this factor does not seem to be an important one in determining the distinctive characteristics of the recorded curve. In leads from the endocardial surface of the heart it is not present, and Lewis and Rothschild found that flooding the pericardium with blood did not materially alter the time of the chief deflections obtained by leading from the immersed epicardial surface. Between direct and semidirect leads there can, therefore, hardly be any fundamental difference. In the latter, as compared to the former, the exploring electrode is more distant from the heart as a whole. Its distance from the nearest muscle units is absolutely greater and relatively greater in comparison with its distance from other parts of the heart. The potential of the indifferent electrode exercises a relatively larger influence in semidirect than in direct leads. Apparently, these are the only respects in which the two methods of leading differ materially. Suppose that we were to start with a direct lead and gradually move the exploring electrode away from the surface of the heart, electrical contact being maintained by surrounding heart and electrode with a medium of approximately the same specific conductivity as the body tissues. The form and amplitude of the recorded deflections must then change in a continuous manner; rapidly at first, but more gradually as the distance of the electrode from the heart increases. Since moving the exploring electrode away from the heart tends to decrease the influence exerted by the muscle units with which it was originally in contact and to increase relatively the influence of the muscle units lying adjacent to them, it is clear that when the area of cardiac surface over which similar potential variations occur simultaneously is extensive all resemblance between the deflections of the direct and those of the final semidirect lead will not be lost until the distance of the exploring electrode from the heart is comparatively great.*

This line of thought and the character of the ventricular deflections in precordial leads led us to suspect that there might be a close relation between the form of these deflections and those which would be obtained by leading directly from the underlying portions of the ventricular wall; and consequently that, by the use of such leads, the general order of ventricular excitation in man might be determined directly. Even if this suspicion should prove unwarranted, it seemed probable that a comparison of the ventricular deflections obtained by semidirect leads in

*The fundamental principle involved here has been discussed by Jeans: "The Mathematical Theory of Electricity and Magnetism," ed. 4, Cambridge University Press, 1923, p. 70.

animals with those obtained by similar leads in man might throw considerable light upon the interpretation of the human electrocardiogram.

EXPERIMENTAL OBSERVATIONS

General Methods.—In the experiments to be described we employed dogs of large size. They were fully anesthetized with sodium amytal given intravenously.* The heart was exposed by splitting the sternum and opening the pericardial sac. The electrodes employed for standard indirect leads were small copper disks sewed under the skin; for direct and semidirect leads we used glass tubes of 3 or 4 mm. bore stoppered at one end with salted kaolin or gelatin and filled with copper sulphate solution into which a bright copper wire was thrust. The actual contact with the heart in direct leads was made by fat-free wool partially imbedded in the kaolin or gelatin plug and moistened with normal salt or Ringer's solution. To hold this in place and to protect the surface of the heart from injury a small piece of soft rubber tubing was slipped over the end of the glass tube.†

Two Einthoven galvanometers coupled together in tandem enabled us to take a direct or semidirect lead and a standard indirect lead simultaneously. In taking the former the exploring electrode was attached to the right-hand terminal of the galvanometer; the indifferent electrode was placed on the left hind leg. The arrangement was therefore such that relative negativity of the exploring electrode produced an upward deflection in the completed curve. Lead I was used as the standard lead; in recording this the galvanometer was employed at the normal sensitivity; a deflection of 1 cm. per millivolt. For the direct or semidirect leads the sensitivity of the galvanometer varied in different instances from one-fourth to one-twentieth of the normal.

To produce bundle-branch block we employed the method used by Lewis,[5] and by Wilson and Herrmann;[6] a small knife blade was thrust through the ventricular wall and the bundle branch cut or injured by pressure with the back of the blade. The location of the cut or injury was determined at the end of the experiment.

For measuring the time intervals of our curves we have employed the record measuring machine devised by Captain B. H. Elliott and manufactured by the Cambridge Instrument Company.

A Typical Experiment.—We may describe as typical of our usual method of procedure an experiment performed on January 24, 1930. The dog was a large bull terrier. Fig. 1 (Curve 621) shows Leads I and III taken simultaneously before the chest was opened. The heart was fully exposed in the usual way and then covered completely with

*In our experiments this drug produced almost complete vagal paralysis.

†Such electrodes are not, as is often supposed, strictly nonpolarizable. If two of them are placed in contact wtih copper sulphate solution and connected with the terminals of the string galvanometer, an e.m.f. of ten millivolts suddenly introduced into the circuit will cause evident overshooting due to polarization capacity. This effect is less pronounced the greater the area of the surface of contact between metal and solution.

a large pad of gauze, about 1.5 cm. in thickness, soaked in warm normal salt solution. A series of curves was then taken by leading from various points on this pad to the left leg. (Fig. 2, left hand column.) Through an error in attaching the lead wires these curves were taken in such a way that relative negativity of the leg electrode rather than the exploring electrode yielded an upward deflection. In taking the first curve the exploring electrode was placed in contact with that part of the pad which rested upon the right basal margin of the heart. With each succeeding curve it was moved downward and to the left toward the cardiac apex a distance of approximately 2 cm. The final curve was taken from that part of the pad which lay upon the apex of the left ventricle. The galvanometer was employed at one-fifth the normal sensitivity; that is

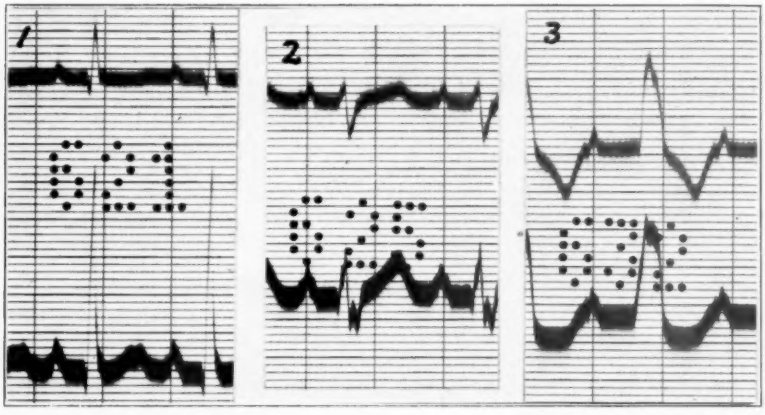

Fig. 1.—Experiment of Jan. 24, 1930. No. 621: Leads I and III before opening the dog's chest. No. 625: Leads I and III after pressure upon the right branch of the His bundle. No. 632: Leads I and III after section of the left branch of the His bundle.

to say, the tension of the string was so adjusted that 10 millivolts produced a deflection of 2 cm.

After this series of curves was obtained, the pad was removed and two attempts were made to produce right branch block by pressing upon the right branch of the His bundle with the back of a small knife blade thrust through the wall of the conus just below the pulmonary valve. The second attempt was apparently successful; the resulting change in the form of the electrocardiogram in Leads I and III is shown in Fig. 1 (Curve 625). The heart was again covered with the gauze pad and an-

Fig. 2.—Experiment of Jan. 24, 1930. Each column shows a series of five semidirect leads taken through a pad of gauze placed upon the exposed heart and recorded simultaneously with Lead I. Left-hand column: Taken while the cardiac mechanism was normal. The semidirect leads are upside down (see text). The sensitivity of the galvanometer was normal for Lead I and one-fifth normal for the semidirect leads. Middle column: Right branch block is present. The sensitivity of the galvanometer was one-fourth normal for the semidirect leads. Right-hand column: Left branch block is present. The sensitivity of the galvanometer was one-fifth normal for the first three and one-twentieth normal for the last two semidirect leads. The number on each curve gives the interval in seconds by which the chief upstroke of the semidirect lead follows the onset of R in Lead I. The time marks on the curves indicate intervals of 0.2 second.

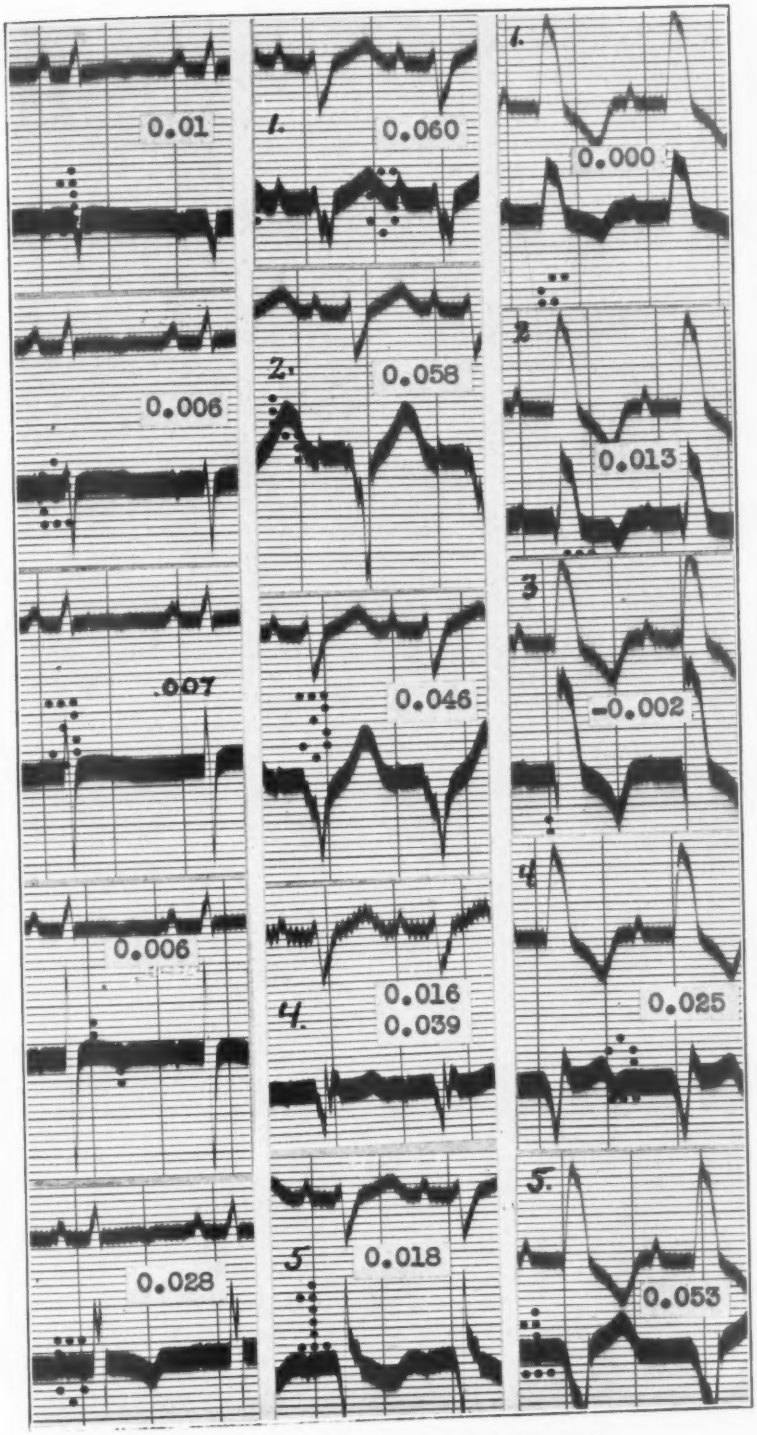

Fig. 2. (See legend on opposite page.)

other series of semidirect leads was taken in the same manner as before, except that the lead wires were now properly connected so that relative negativity of the exploring electrode produced an upward deflection. These curves are shown in Fig. 2 (middle column). Of the five curves taken only the last was from that part of the pad overlying the left ventricle. The part of the pad from which the first curve was taken lay beyond the atrioventricular groove. The galvanometer was used at one-fourth the normal sensitivity.

Shortly after these curves were taken the right branch of the His bundle began to recover and within a few minutes the electrocardiogram had returned to the normal type. Two attempts were then made to cut the left branch; the second was apparently successful; the form of the resulting electrocardiogram in Leads I and III is shown in Fig. 1 (Curve 632). The gauze pad was then reapplied and a third series of semidirect leads was taken as before. The first three curves were taken with the galvanometer at one-fifth the normal sensitivity; in taking the last two curves, however, the sensitivity was reduced to one-twentieth normal in order to keep the large downward deflections of the semidirect and the upward deflections of the standard lead both on the narrow film.

A short time after these curves were taken complete heart-block developed; the heart gradually dilated and the animal died. Examination of the right side of the ventricular septum showed two large subendocardial hemorrhages, one on either side of the main stem of the right bundle branch about one centimeter above the base of the anterior papillary muscle. Examination of the left side of the septum showed a deep gash which obviously severed the main stem of the left bundle branch completely. It lay just beneath the aortic valve and one of the valve cusps had been cut at its base. The resulting high-grade aortic insufficiency was probably partly responsible for the final dilatation of the heart.

Additional Observations.—In Fig. 3 we show some curves taken during an experiment performed on January 17, 1930. Curve 602 shows Leads I and III taken after section of the left bundle-branch just below the aortic valves. Curve 603 shows Lead I and a direct lead from the right central region; Curve 604 shows Lead I and a direct lead from the left apex. After these curves were made the heart was covered with a pad of gauze soaked in warm normal salt solution and a series of five semidirect leads was taken as in the experiment previously described. The curves shown in Fig. 3 (Curves 605-1-3-5) are the first, third, and fifth of this series. The sensitivity of the galvanometer was unfortunately not recorded; it was probably one-tenth or one-twentieth normal for the direct leads and one-fourth or one-fifth normal for the semidirect leads. The indifferent electrode was placed on the left hind leg.

Description of Experimental Curves.—With regard to the form and amplitude of the curves which they obtained by leading directly from the ventricular muscle to the chest wall, Lewis and Rothschild[3] make

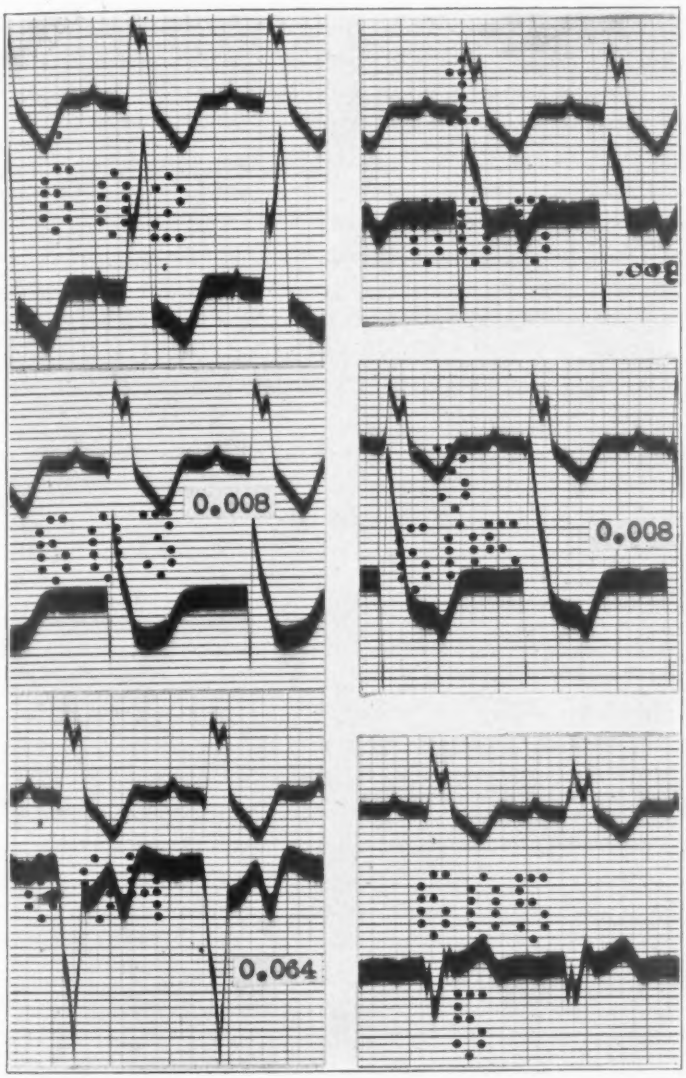

Fig. 3.—Experiment of Jan. 17, 1930. No. 602: Leads I and III after section of the left branch of the His bundle. No. 603: Lead I and a direct lead from the right central region. No. 604: Lead I and a direct lead from the left apex. No. 605: 1, 3, 5: The first, third and fifth of a series of five semidirect leads taken through a pad of gauze placed upon the heart.

the following statement: "The form of the curves taken directly from the ventricle by a single contact is variable. The majority of such curves show an initial dip of variable extent (2-35 millivolts). This dip is relatively slow and usually unbroken, but it may be notched; it

represents the first or extrinsic deflection. There may be a return to the base line before the intrinsic deflection is recorded, but more commonly, the onset of the intrinsic deflection terminates the dip. The upstroke is always very abrupt, and the recorded image of the fiber is consequently faint. Its amplitude, measured from its point of origin, is always considerable (10-80 millivolts)."

The curves obtained by semidirect leads may be described in very similar terms. These curves also show an initial dip of variable extent (1-20 millivolts), which is relatively slow and may be unbroken or notched. It is sometimes preceded by a small upright deflection and this is also true of the corresponding deflection of direct leads. This initial dip is followed by an abrupt upward movement of considerable amplitude (5-20 millivolts), which is ordinarily the steepest deflection of the ventricular complex. When this chief upstroke occurs early, it usually carries the string far above the base line; in such cases the initial downward movement is ordinarily of small amplitude, but there are occasional exceptions to this rule. When the chief upstroke occurs late, it usually carries the string only to the base line or a little way beyond it; in such cases the initial downward movement is of large amplitude. Although the upstroke under consideration is generally by far the sharpest deflection of the ventricular complex, being depicted by the thinnest line because it is written by the most rapid movement of the string, it is sometimes little, if at all, steeper than the other deflections. In some instances no deflection of this character is present.

The chief difference between the curves obtained by direct leads and those obtained by semidirect leads lies in the voltages which are on the average much greater in the former. There is also a difference in the relative steepness of the chief upstroke which is greater in direct leads, permitting the more certain identification of this deflection.

We may now examine the curves illustrated in Figs. 2 and 3 in greater detail. In the case of the undamaged heart (Fig. 2, first column), the curves from that part of the gauze pad which lay upon the right ventricle (2, 3, and 4) show a chief upstroke (actually a downstroke because of the error in connecting the lead wires previously mentioned) which comes early, about 0.007 second after the onset of R in Lead I. In the single curve (5), taken from that part of the pad which lay upon the left apex, this deflection comes a little later; about 0.028 second after R. In the first curve, which was taken from that part of the pad which lay above the atrioventricular groove, the ventricular deflections are small.

When right branch block was present, the chief upstroke of those curves which were taken from that part of the pad which lay upon the right ventricle (2, 3, and 4) begins late; about 0.05 or 0.06 second after the onset of R in Lead I. The single curve taken from that part of the

pad which lay upon the left apex (5), on the other hand, shows an early chief upstroke, which begins about 0.018 second after the onset of R. In the fourth curve of this series the chief upstroke is early (0.016 after R), but of small amplitude; a second smaller and more gradual upstroke occurs late (0.39 second after R). It may be pointed out here that curves of transitional type were frequently obtained from that part of the pad which lay near the interventricular groove; in such curves there were sometimes two prominent upstrokes, one early, the other late; in other instances there was no chief upstroke at all; and in still others the chief upstroke fell in a position intermediate between its position in the curves taken more toward the right base and that which it occupied in those taken more toward the left apex. It will be noted that the chief upstrokes of the first three curves of this series do not rise above the base line; the ventricular complexes resemble in general form the ventricular complexes of Lead I.

Turning now to the left branch block series, we find that in those curves (1, 2, and 3) obtained by leading from portions of the pad that lay upon the right ventricle the chief upstroke is early (practically synchronous with R of Lead I) and carries the fiber far above the base line where it remains throughout the remainder of the QRS interval. These complexes resemble in general form the ventricular complexes of Lead I. In the last curve of the series (5), which was taken from that part of the pad which lay upon the left apex, the chief upstroke is late (0.053 second after R) and rises only a little way above the base line, so that the ventricular complex is of the opposite type. The fourth curve is of the transitional type; the chief upstroke occurs about 0.025 second after R.

The curves shown in Fig. 3, which were obtained from a second animal with left branch block, may be compared with those just described. The complexes obtained by leading directly from the right central region (Curve 603) and those obtained by semidirect leads from that part of the pad which lay upon the right ventricle (Curves 605-1-3) are very similar in form. The chief upstroke occurs at approximately the same time in both. The resemblance between the complexes obtained by leading directly from the left ventricle and those obtained from that part of the pad which lay upon it is less striking. The latter complexes are of the transitional type.

Comments.—The experiments described show without question that when bundle-branch block is present the chief upstroke of the ventricular complex in semidirect leads is early when the exploring electrode is placed close to the ventral surface of the contralateral ventricle and late when this electrode is placed close to the surface of the homolateral ventricle. In the former case the fiber usually remains above, in the latter case it usually remains below the base line throughout the greater

part of the QRS interval. During the period of ventricular excitation the mean potential of points near the ventral surface of the contralateral ventricle is usually negative, the mean potential of points near the surface of the homolateral ventricle is usually positive.

We have not attempted to free our experimental curves from effects produced by variations in the potential of the indifferent electrode. The sensitivity of the galvanometer was never increased beyond one-fourth the normal, and the amplitude of the chief deflections of the ventricular complex in semidirect leads of the type employed is so great, when measured in millivolts, in comparison with that of the chief ventricular deflections of standard leads that the subtraction from each ordinate of one-third the sum of the deflections inscribed in Leads II and III at the corresponding instant in the cardiac cycle could not materially alter their form or the time of their occurrence.

Significance of the Chief Ventricular Upstroke in Semidirect Leads.—It is difficult to avoid the conclusion that the chief upstroke of the ventricular complex in semidirect leads of the kind under consideration corresponds to the intrinsic deflection of direct leads, and that its onset marks the excitation of that portion of the ventricular surface which lies nearest the exploring electrode. While this conclusion is in no way essential to the main thesis of the present article, which is concerned only with a comparison of results obtained by similar methods of leading in animals and in man, it is sufficiently important to merit a brief consideration of certain observations with which it does not seem to be in accord.

The experiments which Lewis and his collaborators[3, 7] carried out to show that the intrinsic deflection of direct leads signals the arrival of the excitatory process beneath the exploring electrode suggest that no similar deflection can be expected to occur in leads in which this electrode is not in actual contact with the heart muscle. The intrinsic deflection was first identified in leads in which both electrodes were placed upon the auricular surface along a line radiating from the sinus node, the galvanometer connections being made in such a way that relative negativity of the proximal electrode (that nearest the node) produced an upward deflection. It was shown that when the electrodes were placed near the tip of the right auricular appendix the intrinsic deflection disappeared when the base of the appendix was crushed in such a way as to prevent the excitatory process from progressing beneath them; the first extrinsic deflection, on the other hand, remained. It was also shown that when the electrodes were moved along a line stretching from the sinus node up the superior or down the inferior vena cava the intrinsic deflection disappeared at the moment that the proximal electrode passed the border of the muscle which surrounds each of these vessels near its orifice.

With reference to the intrinsic deflection in direct leads from the ventricle, in which only one electrode (the exploring electrode) was placed upon the muscle, the other (the indifferent electrode) being in contact with the chest wall, it was shown that the time of this deflection, with reference to the deflections of Lead II, was not altered by moving the indifferent electrode. It was also demonstrated that the intrinsic deflection fell later and later as the exploring electrode was moved up the conus arteriosus, and that it disappeared when the muscle boundary at the junction of conus and pulmonary artery was crossed.

We have repeated these last experiments. In leads from the conus arteriosus the ventricular complex ordinarily begins with a small upward deflection followed by a sharp and deep dip. This dip is terminated by the onset of the intrinsic deflection which carries the string back to the base line or a little way beyond it. The intrinsic deflection is late. When the exploring electrode is moved across the muscle border on to the pulmonary artery, the form of the ventricular complex changes and the chief upstroke is early. This procedure is not equivalent to moving the exploring electrode away from the heart along a line normal to its surface, for it involves placing this electrode opposite an opening, the valve orifice, in the ventricular wall. We have pointed out elsewhere[8] that the potential of any point in the body, in so far as it is influenced by the heart beat, is determined theoretically according to the following equation:

$$V = \Phi\Omega$$

where V is the potential of the point; Φ, a constant; and Ω, the solid angle subtended at this point by the surface which separates active from resting muscle. This angle is positive or negative according as the positive or the negative side (resting or active side) of the surface in question faces toward the apex of the cone which defines it. Throughout the greater part of the QRS interval a point on the pulmonary artery near the valve and one on the conus arteriosus must lie on opposite sides of this surface and must have potentials unlike in sign. The former facing toward the interior of the heart is on the negative side; it becomes negative early and remains so until the greater part of the ventricular muscle has passed into the active state. The latter remains negative only until the activation of the subendocardial muscle of the conus places it on the positive side of the active-resting surface.

Lewis and Rothschild[3] mention that when the exploring electrode is introduced into the ventricular cavity an early reading (i.e., an early intrinsic deflection) is obtained even when the electrode is not in contact with the endocardial surface of the heart except through the blood. This observation, which we have also made, indicates that intrinsic or intrinsic-like deflections are, in the case of the ventricular muscle, by no means peculiar to direct leads.

In the case of the auricular muscle semidirect leads yield no sharp deflections. We have pointed out that when, starting with a direct lead, we move the exploring electrode away from the heart wall through a conducting medium, we tend to decrease the influence of the muscle units with which it was originally in contact and to increase relatively the influence of the muscle units that surround them. The effect must be somewhat, although not exactly, the same as that produced by increasing the size of the electrode. It is clear that the potential of the electrode at any instant must be determined by the mean potential of the area with which it is in contact. If the potential of some points of this area is changing in one direction and the potential of other points is changing in the opposite direction the potential of the exploring electrode may remain nearly stationary. In the case of the auricle, increasing the size of the exploring electrode causes a rapid degradation of the recorded curve with a disappearance of all sharp deflections, because such neighboring points as are arranged radially with reference to the sinus node pass through similar changes in potential, not simultaneously but in succession, displaying similar potentials when they bear a similar relation to the crest of the excitation wave. No similar effect occurs in the case of the ventricle. Here the excitatory process spreads outward through the ventricular wall and all points over relatively large areas pass through similar potential levels at the same time. At any instant the average potential over a small area and the average potential over a large area are therefore very nearly equal.

CLINICAL OBSERVATIONS

For precordial leads we employed small copper disks, about one inch in diameter, which were soldered to binding posts. The skin was cleaned with alcohol and with soap and water. The electrodes were smeared with a commercial preparation manufactured for use in diathermy treatments and were held in place with adhesive tape. Four or five electrodes were arranged diagonally across the precordium, the first being placed, as a rule, to the right of the sternum in the third or fourth intercostal space near the right border of cardiac dullness, and the last beyond the left border of dullness in the region of the apex beat. The indifferent electrode was placed on the left leg. The galvanometer was employed at approximately one-half the normal sensitivity and Lead I was recorded simultaneously with each precordial lead.

The exploring electrode was, of course, considerably further from the surface of the heart in these leads than in the semidirect leads employed in our animal experiments. In order not to increase the distance to an extent that would make comparison hazardous, we chose, in so far as possible, patients of slight build, avoiding the obese and the emphysematous. It should be noted that the left ventricle is much less favor-

ably situated for our purpose than the right. The surface which it presents anteriorly is small in extent and is covered by a relatively thick layer of tissue. Leads from the central precordium, which overlies the anterior surface of the right ventricle, are therefore of more value for comparison with the experimental leads than those from the region of the apex beat or beyond. It is naturally not possible to say precisely where the interventricular groove lies with reference to the landmarks of the anterior chest wall in any given case, since this must depend upon

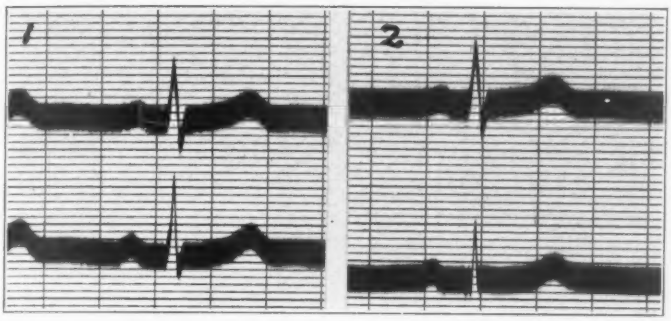

Fig. 4.—Case 1. Leads I and II on the left; Leads I and III on the right. The electrocardiogram is of the normal type.

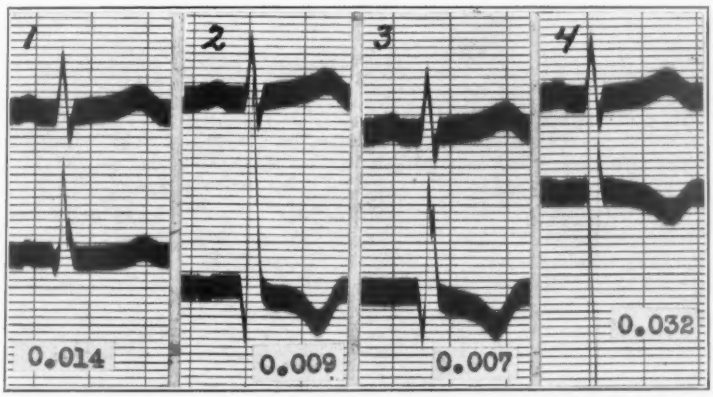

Fig. 5.—Case 1. A series of four precordial leads, each recorded simultaneously with Lead I. The introduction of one millivolt into the circuit produced a deflection of 7 mm. in semidirect Leads I and III, and of 8 mm. in semidirect Leads II and IV.

the position of the heart and the relative size of the two ventricles. By arranging a number of electrodes along a line approximately at right angles to this groove, this difficulty is to a large extent avoided. It is possible, however, that in some instances our line of electrodes was not extended sufficiently far to the left to obtain semidirect leads from the left ventricular surface.

Case 1.—The patient was a boy, aged seventeen years, who gave a history of rheumatic fever and chorea. On examination there was questionable slight enlargement of the heart and a soft systolic murmur at the apex and at the base.

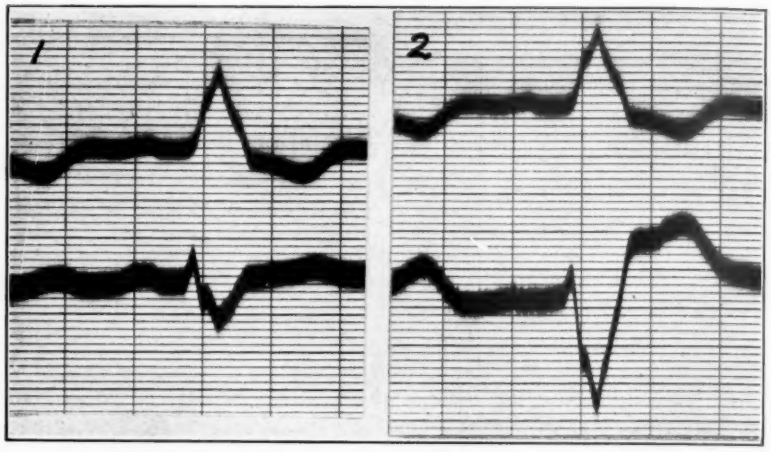

Fig. 6.—Case 2. Leads I and II are shown on the right, and Leads I and III on the left. Typical bundle-branch block of the common type with a QRS interval of 0.169 second.

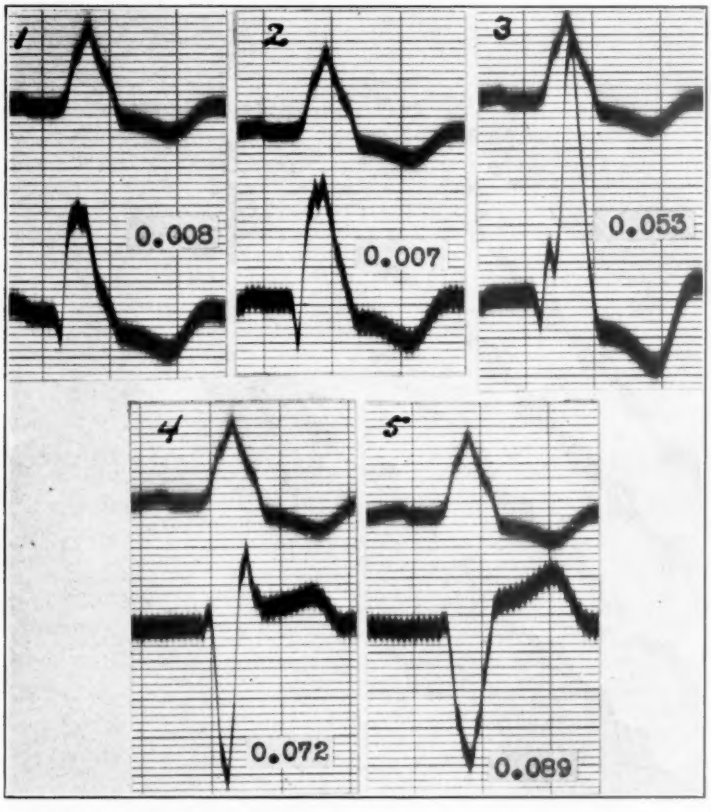

Fig. 7.—Case 2. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 7 mm. in Lead I, 5 mm. in Lead II, 8.5 mm. in Lead III, 6 mm. in Lead IV, and 5 mm. in Lead V.

There was a third sound in early diastole at the apex. Slight rheumatic involvement of the mitral valve was suspected. The electrocardiogram was of the normal type (Fig. 4). Four precordial leads were taken: (1) from the right sternal edge at the fourth costal cartilage; (2) from the left sternal edge at the fourth costal cartilage; (3) from a point midway between (2) and (4); (4) from the fifth intercostal space just beyond the nipple line. The curves are shown in Fig. 5; in the first three the onset of the chief upstroke is relatively early (0.007 to 0.014 second after the onset of R in Lead I) and the preliminary downward movement of the fiber is of small amplitude. In the fourth curve the downward movement is large and the upstroke is later (0.032 second after R). These curves may be compared with those shown in the left-hand column of Fig. 2.

CASE 2.—The patient was a man, aged sixty-one years, with a history of long standing hypertension (systolic blood pressure—225 mm. Hg) and cardiac weakness with shortness of breath, engorgement of the liver, and edema. The heart was greatly enlarged; there were no valve lesions. The electrocardiogram showed typical bundle-branch block of the common type (Fig. 6) with a QRS interval of approximately 0.169 second. A series of five precordial leads was taken: (1) from the right sternal edge in the fourth intercostal space; (2) from the left sternal

TABLE I (CASE 2)

TIME	V_F	$-V_1+V_F$	$-V_1$	$-V_5+V_F$	$-V_5$	I	II	II (CAL)	III	α DEGREES
0.0	0.0	0.0	0.0	0.0	0.0	0.0	−2.9	0.0	0.0	–
0.0062	1.0	−2.0	−3.0	0.0	−1.0	0.0	0.0	1.5	1.5	90
0.0124	3.1	−9.0	−12.1	0.0	−3.1	0.0	4.4	4.6	4.6	90
0.0186	5.6	−19.0	−24.6	10.0	4.4	1.5	10.2	9.2	7.7	81
0.0248	8.4	−10.0	−18.4	11.7	3.3	3.9	12.5	14.6	10.7	75
0.0310	3.3	12.0	8.7	−1.7	−5.0	6.9	8.1	8.4	1.5	39
0.0372	2.3	55.0	52.7	−17.0	−19.3	11.5	0.7	2.3	−9.2	−21
0.0434	−11.1	75.0	86.1	−51.5	−40.4	19.2	−7.3	−7.0	−26.2	−45
0.0496	−18.2	84.0	102.2	−86.6	−68.4	25.4	−14.7	−14.6	−40.0	−51
0.0558	−21.3	87.0	108.3	−115.0	−93.7	30.0	−16.2	−17.0	−47.0	−51
0.0620	−21.0	91.0	112.0	−137.0	−116.0	32.4	−13.9	−15.3	−47.7	−48
0.0682	−22.1	103.0	125.1	−153.0	−130.9	33.8	−14.7	−16.2	−50.0	−48
0.0744	−24.7	91.5	116.2	−176.0	−151.3	37.0	−17.6	−18.5	−55.5	−49
0.0806	−27.5	92.0	119.5	−195.0	−167.5	42.5	−21.3	−20.0	−62.5	−48
0.0868	−32.4	94.5	126.9	−198.0	−165.6	47.7	−22.8	−24.8	−72.5	−50
0.0940	−36.8	91.0	127.8	−202.0	−165.2	51.6	−29.4	−29.4	−81.0	−51
0.1002	−39.3	83.0	122.3	−218.0	−178.7	50.0	−30.2	−34.0	−84.0	−54
0.1064	−36.4	72.0	108.4	−198.0	−161.6	44.7	−28.6	−32.3	−77.0	−55
0.1126	−33.8	55.0	88.8	−183.0	−149.2	40.0	−26.5	−30.7	−70.7	−56
0.1188	−31.2	45.0	76.2	−170.0	−138.8	35.4	−24.3	−29.6	−64.0	−58
0.1250	−26.5	34.0	60.5	−137.0	−110.5	31.6	−22.0	−23.9	−55.5	−56
0.1312	−24.6	26.0	50.6	−113.0	−88.4	26.2	−20.6	−23.8	−50.0	−58
0.1374	−21.5	21.0	42.5	−85.0	−63.5	21.6	−18.4	−21.4	−43.0	−60
0.1436	−18.4	16.0	34.4	−63.2	−44.8	20.0	−15.4	−17.6	−37.6	−58
0.1498	−13.6	11.0	24.6	−48.2	−34.6	17.7	−12.5	−11.5	−29.2	−53
0.1560	−10.9	6.0	16.9	−25.0	−14.1	15.4	−10.3	−8.2	−24.6	−49
0.1620	−9.5	1.0	10.5	−6.7	2.8	13.1	−7.3	−7.7	−20.8	−51
0.1682	−5.9	−4.0	1.9	16.7	22.6	8.5	−6.6	−4.6	−13.1	−50
0.1744	−1.7	−9.0	−7.3	40.0	41.7	2.3	−2.9	−1.5	−3.8	−53
0.1806	−0.2	−15.0	−14.8	43.0	43.2	−2.3	−0.7	−1.5	0.8	−170
0.1868	3.8	−18.0	−21.8	45.0	41.2	−5.4	0.0	3.1	8.5	129

The measurements are expressed in units of 0.02 millivolt. V_F is the potential of the left leg. $-V_1+V_F$ is precordial Lead I as recorded. $-V_1$ is minus the potential of precordial point 1. $-V_5+V_F$ is precordial Lead V as recorded. $-V_5$ is minus the potential of precordial point 5. II (cal) is Lead II calculated by the addition of Leads I and III.

edge in the fifth intercostal space; (3) from the sixth rib in the midclavicular line; (4) from the sixth intercostal space 2.5 cm. medial to the anterior axillary line, and (5) from the seventh rib in the anterior axillary line. These curves are shown in Fig. 7; in the first two the chief upstroke is early (about 0.007-0.008 second after the onset of R in Lead I) and the complexes resemble those of Lead I in form. In the third curve the main upstroke is deeply notched; the chief upward movement occurs about 0.053 second after R. In the last two curves the chief upstroke is late (0.072 to 0.089 second after R) and rises only a little way above the base line.

In order to show that potential variations of the indifferent electrode were not an important factor in determining the form of the ventricular complexes of these precordial leads we have computed the potential variations of the first and fifth points investigated. The numerical data are given in Table I. The original curves were enlarged about five diameters by optical projection, traced on coördinate paper, and measured. All measurements are expressed in units of 0.02 millivolt. We give the potential values corresponding to instants separated by equal time intervals. The table gives in order the potential of the left leg (V_F); the recorded and corrected potentials of Points 1 and 5; and the measurements of the ventricular complexes of the standard leads. In the case of Lead II we give both the measurements of the recorded curve and the values calculated by adding the deflections of Leads I and III. In the last column of the table the angle α which defines the position of the electrical axis is given. It will be noted that during the early part of the QRS interval there is a counter-clockwise rotation of the electrical axis of the type described by Lewis[5] in cases of branch block of the common type. While the potential variations of the indifferent electrode are by no means without influence upon the form of the precordial curves, the elimination of this influence does not materially alter the general outline of the ventricular complex or the time of occurrence of the chief upstroke.

TABLE II

CASE 3						CASE 7	
TIME	V_F	$-V_3+V_F$	$-V_3$	$-V_4+V_F$	$-V_4$	TIME	V_F
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.008	0.6	–10.0	–10.6	–4.0	–4.6	0.0098	–0.6
0.016	4.0	–34.0	–38.0	–16.0	–20.0	0.0196	–0.6
0.024	4.6	–56.0	–60.6	–34.0	–38.6	0.0294	2.3
0.032	3.3	–70.0	–73.3	–50.0	–53.3	0.0392	16.0
0.040	–4.0	–84.0	–80.0	–66.0	–62.0	0.0490	54.0
0.048	–18.3	–94.0	–75.7	–80.0	–61.7	0.0588	78.0
0.056	–29.6	–76.0	–46.4	–82.0	–52.4	0.0686	85.0
0.064	–28.0	–10.0	18.0	–82.0	–54.0	0.0784	62.0
0.072	–29.0	16.0	45.0	–84.0	–55.0	0.0882	33.3
0.080	–34.0	40.0	74.0	–86.0	–52.0	0.0980	5.3
0.088	–41.3	30.0	71.3	–90.0	–48.7	0.1078	–5.0
0.096	–53.3	–26.0	27.3	–78.0	–24.7	0.1176	–15.0
0.104	–51.0	–40.0	11.0	–50.0	1.0	0.1274	–12.6
0.112	–39.0	–16.0	23.0	–26.0	13.0		
0.120	–29.6	0.0	29.6	0.0	29.6		
0.128	–9.0	2.0	11.0	10.0	19.0		
0.136	–0.6	4.0	4.6	16.0	16.6		
0.144	0.6	4.0	3.4	18.0	17.4		

All measurements are given in units of 0.02 millivolt.
V_F is the potential of the left leg.
$-V_3+V_F$ is the deflection in precordial Lead III as recorded; $-V_4+V_F$ is the deflection in precordial Lead V as recorded.
V_3 is the potential of precordial point 3; V_4, the potential of precordial point 4.

CASE 3.—The subject was a woman, aged sixty-six years, who complained of palpitation, weakness, and dyspnea. Examination showed a large adenomatous goiter, and conspicuous enlargement of the heart. The blood pressure was moderately elevated (170/60); and there was considerable sclerosis of the peripheral arteries. A systolic and a diastolic murmur were heard in the aortic area and a systolic murmur and gallop rhythm at the apex. There were no signs of cardiac failure.

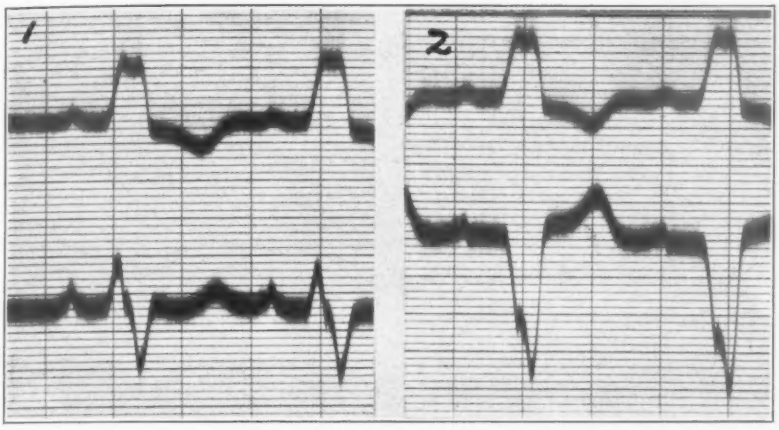

Fig. 8.—Case 3. Leads I and II on the left and Leads I and III on the right. Typical bundle-branch block of the common type. The QRS interval measures 0.134 second.

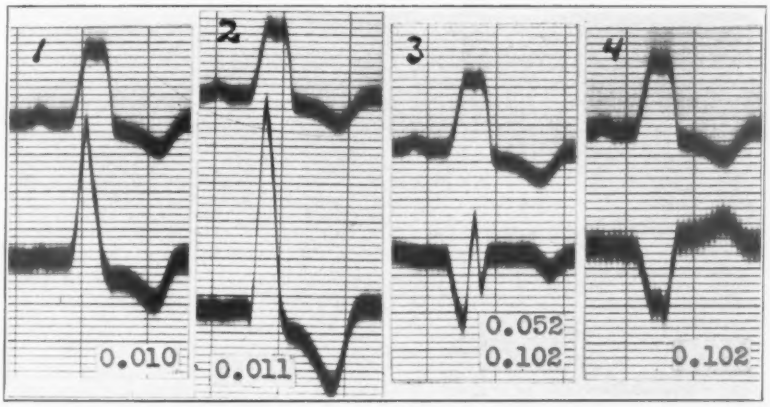

Fig. 9.—Case 3. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 5 mm. in Leads I, II, and IV, and of 4.5 mm. in Lead III.

The electrocardiogram showed typical branch block of the common type (Fig. 8) with a QRS interval of approximately 0.134 second. Four precordial leads were taken: (1) from the fourth intercostal space just to the right of the sternum; (2) from the fourth intercostal space just to the left of the sternum; (3) from the apex (fifth intercostal space, 11 cm. from the midline); (4) from the sixth intercostal space at the anterior axillary line (15 cm. from the midline). These curves are shown in Fig. 9. In the first two leads the chief ventricular upstroke is early (0.01 second after R); the third curve is of the transitional type with two up-

strokes; in the fourth curve the chief upstroke is very late (0.102 second after R) but not particularly sharp. In this case we have computed the potential variations of the third and fourth points investigated. The numerical data appear in Table II. While the recorded ventricular complexes are considerably altered by this cor-

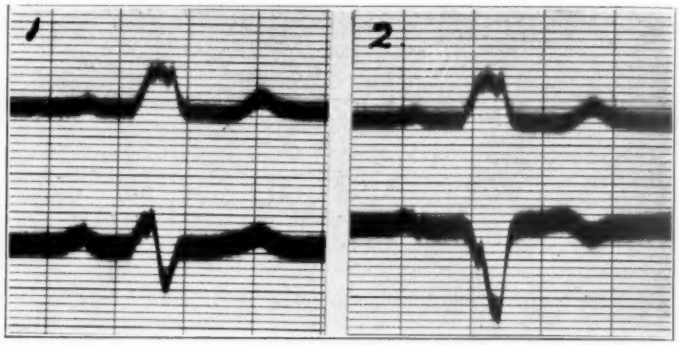

Fig. 10.—Case 4. Leads I and II on the left and Leads I and III on the right. Bundle-branch block of the common type with a QRS interval of 0.146 second.

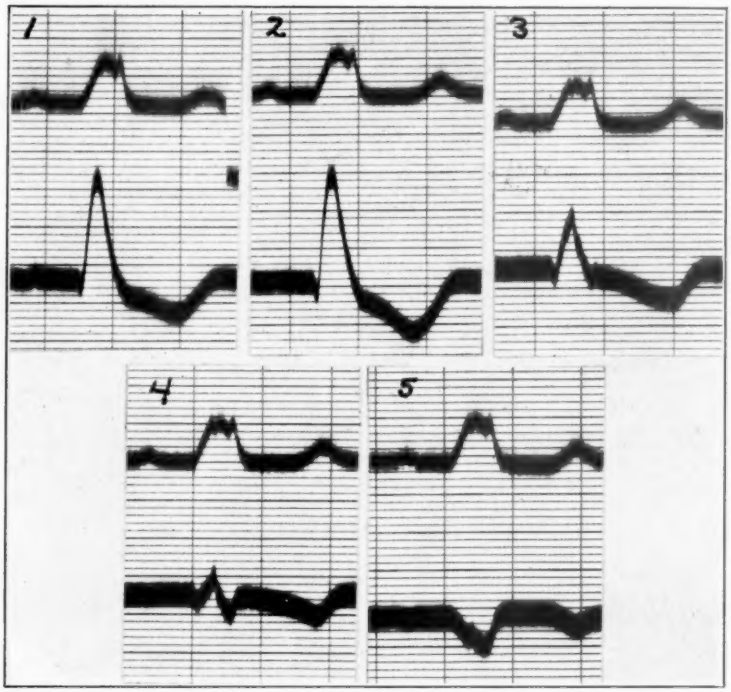

Fig. 11.—Case 4. A series of five precordial leads. In the semidirect leads one millivolt produced a deflection of 5.5 mm. in Lead I, 5 mm. in Leads II, III, IV, and V.

rection, their chief features remain. It is obvious that similar correction could not significantly change the form of the complexes of the first two leads.

Case 4.—The subject was a man, aged sixty-seven years, with general arteriosclerosis. The heart was definitely enlarged; and there was a harsh systolic murmur both at the apex and at the base. The blood pressure was moderately raised

(150/80). There was evidence of mild cardiac weakness. The electrocardiogram showed typical branch block of the common type (Fig. 10) with a QRS interval of 0.146 second. Five precordial leads were taken: (1) from the fifth costal cartilage at the right sternal margin; (2) from the fifth costal cartilage at the left sternal margin; (3) from the fifth intercostal space 4 or 5 cm. from the left sternal margin; (4) from the apex (fifth intercostal space 2 cm. inside the anterior axillary line); (5) from the sixth intercostal space in the anterior axillary line. These curves are shown in Fig. 11; the chief upstroke is obviously early in the first two

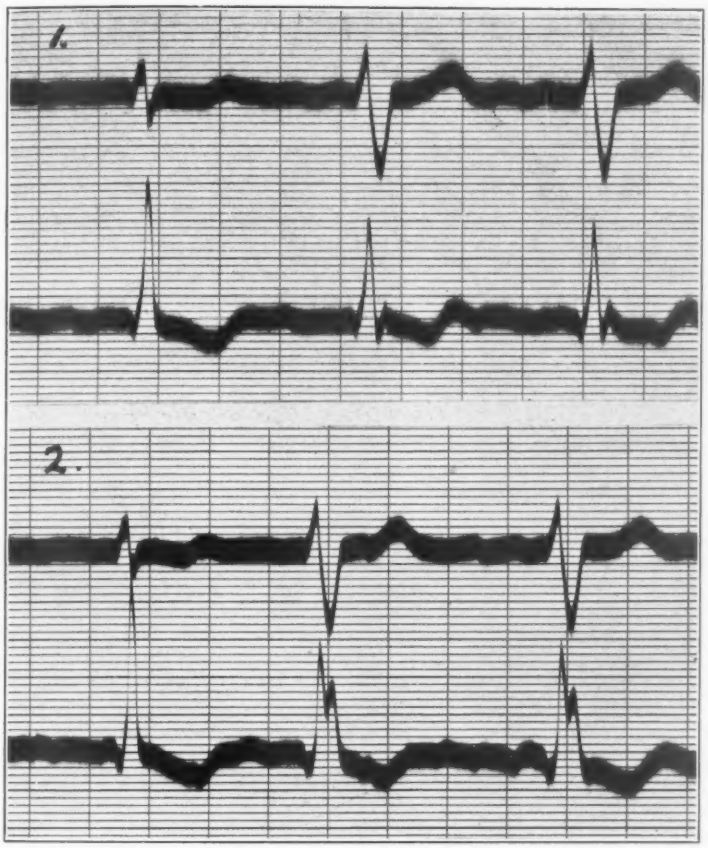

Fig. 12.—Case 5. Leads I and II above, and Leads I and III below. Auricular fibrillation is present. The first complex of each lead is of the normal type. The last two complexes are characteristic of branch block of the rare type. The QRS interval of the narrower complexes measures 0.099 second; that of the broader complexes, 0.135 second.

leads. In the remaining leads the curves are of small amplitude and show no sharp deflections; nevertheless, the principal upstroke is later.

Case 5.—The patient was a boy, aged seventeen years, with typical mitral stenosis and auricular fibrillation. He gave a clear history of rheumatic fever. In the electrocardiogram two types of ventricular complexes occurred; during periods when the heart rate was slow the ventricular complexes were of the type suggesting slight right ventricular preponderance (QRS interval, 0.099 second); whenever the heart rate quickened there was a sudden transition to broad (QRS interval, 0.135 second) diphasic complexes of the type seen in the rare form of branch block

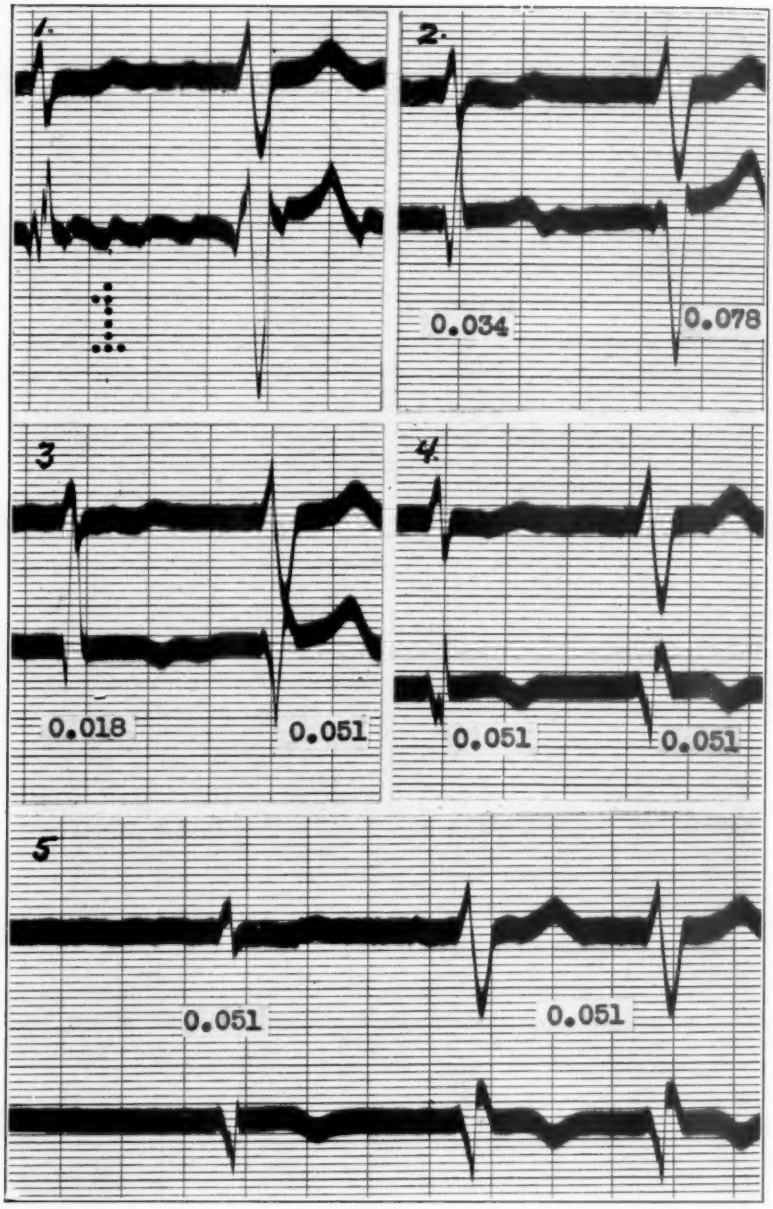

Fig. 13.—Case 5. A series of five precordial leads. The sensitivity of the galvanometer was approximately one-half normal for the first four semidirect leads and one-third normal for the fifth.

(Fig. 12). Five precordial leads were taken: (1) from the fourth intercostal space just to the right of the right border of cardiac dullness (5 cm. to the right of the right sternal margin); (2) from a point just to the left of the middle of the sternum at the level of the fifth costal cartilage; (3) from the fifth intercostal space just to the right of the left nipple line; (4) from the point of maximum pulsation; (5) from the seventh intercostal space in the anterior axillary line and just beyond the maximum impulse. These curves are shown in Fig. 13. In the first lead, which was taken over the right auricle, the auricular oscillations are very prominent. In the second and third leads the chief upstroke is relatively early when the ventricular complexes are of the normal type, and relatively late when they are of the abnormal type. In the last two leads the chief upstroke occurs at about the same time when the ventricular complexes are of the narrow type as when they are of the broad type; it is rather late in both cases. It should be noted that all of the complexes

TABLE III (CASE 5)

TIME	V_F ABNORMAL COMPLEXES	$-V_5+V_F$ ABNORMAL COMPLEXES	$-V_5$ ABNORMAL COMPLEXES	V_F NORMAL COMPLEXES	$-V_5+V_F$ NORMAL COMPLEXES	$-V_5$ NORMAL COMPLEXES
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.009	–3.0	6.0	9.0	0.3	3.0	2.7
0.018	–2.0	7.5	9.5	–0.3	12.0	12.3
0.027	0.0	–6.0	–6.0	–3.0	3.0	6.0
0.036	4.3	–36.0	–40.3	–1.3	–9.0	–7.7
0.045	11.3	–57.0	–68.3	4.0	–27.0	–31.0
0.054	41.3	–96.0	–137.3	15.3	–42.0	–57.3
0.063	25.6	–66.0	–91.6	30.6	–63.0	–93.6
0.072	17.6	54.0	36.4	64.6	–51.0	–115.6
0.081	11.3	60.0	48.7	51.6	45.0	–6.6
0.090	15.3	60.0	44.7	18.6	0.0	–18.6
0.099	17.0	57.0	40.0	2.6	0.0	–2.6
0.108	14.0	39.0	25.0	–0.6	0.0	0.6
0.117	5.6	15.0	9.4	–2.0	0.0	2.0
0.126	1.5	0.0	–1.5			
0.135	–1.0	–6.0	–5.0			
0.144	–2.3	–9.0	–6.7			
0.153	–3.3	–9.0	–5.7			

All measurements are given in units of 0.02 millivolt. V_F is the potential of the left leg. $-V_5 + V_F$ is the deflection in precordial Lead V as recorded. V_5 is the potential of precordial point 5.

of the last precordial lead are of the same form up to the point where the chief upstroke occurs.

We have computed the potential variations of the point from which the last lead was taken. The numerical data are given in Table III. Although correction alters the form of the recorded ventricular complexes of this lead, it does not materially alter the amplitude or time of the chief upstroke.

CASE 6.—The subject was a man, aged sixty-two years, with hypertension (184/120), general arteriosclerosis, enlargement of the heart, and myocardial weakness. No valve lesions were present. The electrocardiogram showed bundle-branch block of the rare type with a QRS interval of 0.14 second. Five precordial leads were taken: (1) from the fifth costal cartilage at the right sternal edge; (2) from the fifth costal cartilage at the left sternal edge; (3) from the fifth intercostal space midway between the left sternal edge and the left midclavicular line; (4) from the fifth intercostal space 3 cm. medial to the anterior axillary line; (5) from the fifth intercostal space at the anterior axillary line. These curves are shown in Fig. 15.

In the first two leads the chief upstroke is late (0.097 second after the onset of R). In the third lead the ventricular complex is of small amplitude. In the last two leads the chief upstroke comes at the time that the peak of R is written and about 0.03 second earlier than the chief upstroke of the first two leads.

CASE 7.—The subject was a woman, aged thirty-two years, with mitral stenosis, who gave a history of rheumatic fever. There were no signs of cardiac failure; the heart was moderately enlarged. The electrocardiogram showed diphasic ventricular

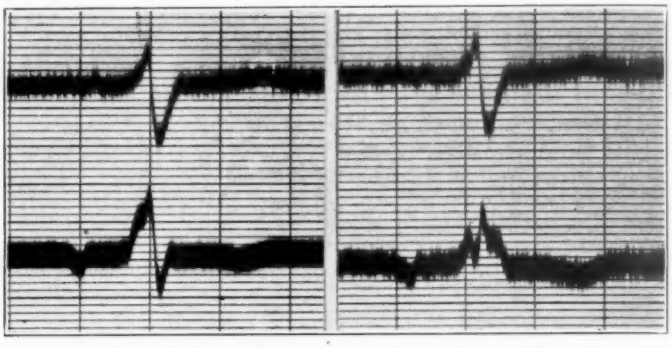

Fig. 14.—Case 6. Leads I and II on the left; Leads I and III on the right. Bundle branch block of the rare type with a QRS interval of 0.14 second.

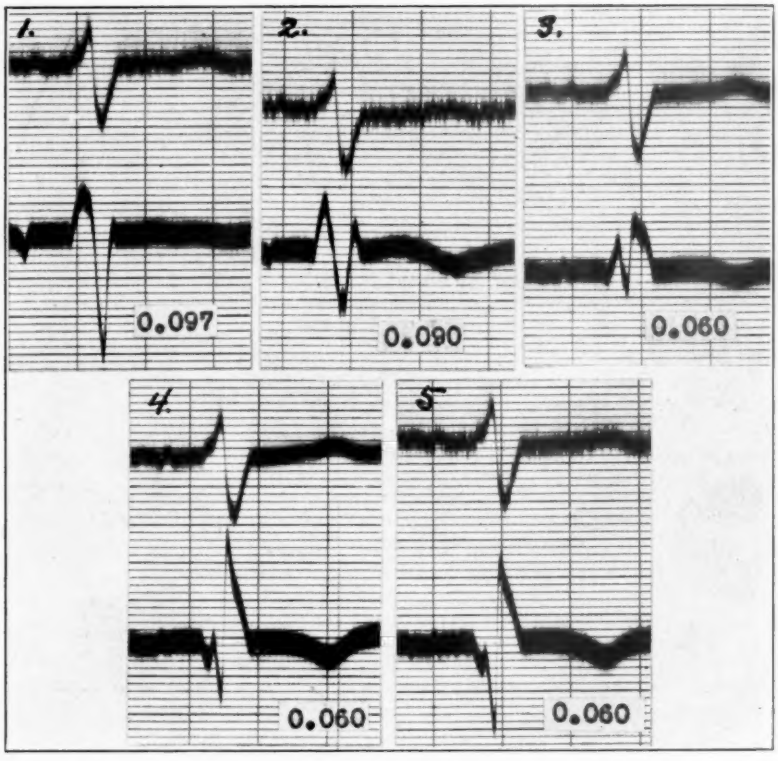

Fig. 15.—Case 6. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 6 to 6.5 mm.

complexes with a QRS interval of 0.105 second. The complexes were not conspicuously notched, but were otherwise strongly suggestive of bundle-branch block of the rare type. Four precordial leads were taken: (1) from the third intercostal space near the right border of the sternum; (2) from the third intercostal space near the left border of the sternum; (3) from the fourth intercostal space 8.5 cm.

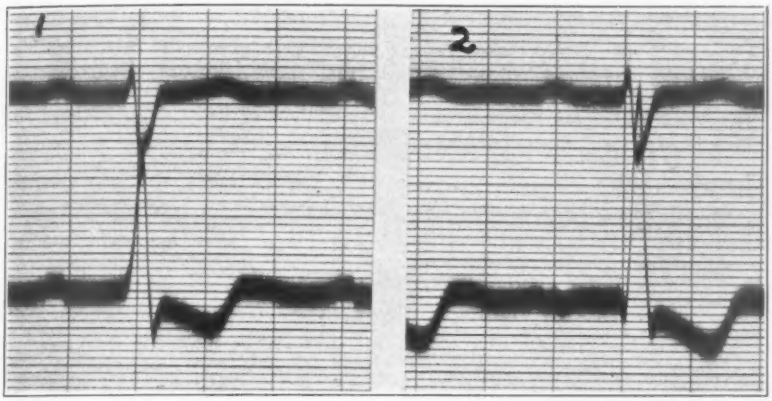

Fig. 16.—Case 7. Leads I and II on the left; Leads I and III on the right. Bundle-branch block of the rare type with a QRS interval of 0.105.

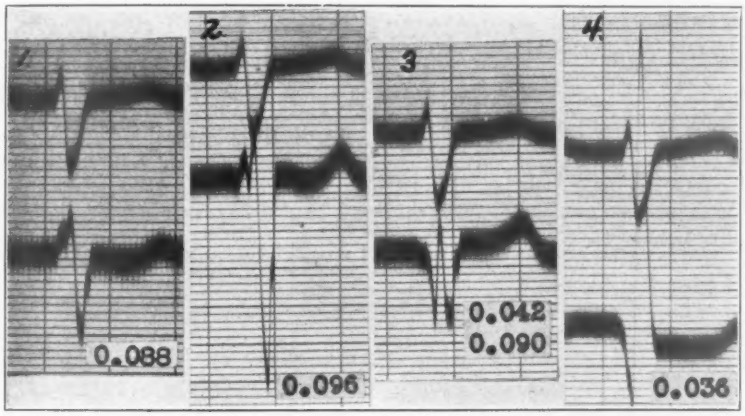

Fig. 17.—A series of four precordial leads each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 5 mm. in Lead I, 9 mm. in Leads II and III. In the case of IV the standardization was not recorded on the film.

to the left of the midline; (4) from the sixth intercostal space near the anterior axillary line. These curves are shown in Fig. 17. In the first two leads, the chief ventricular upstroke is late. The ventricular complex of the third lead is of the transitional type with two principal upstrokes. In the last lead the chief upstroke is relatively early. We have computed the potential variations of the indifferent electrode (Table III); they are too small to alter materially the form of the ventricular complexes or the time or amplitude of the chief upstroke.

Discussion.—In all of the cases of bundle-branch block studied the first leads of the series taken, those from the right and central portions

of the precordium, have yielded ventricular complexes similar to those obtained in the cases described; the chief upstroke of these leads has always been early in the common type of branch block and late in the rare type. These complexes have always resembled those of Lead I in general outline. It should be noted that in so far as the potential variations of the indifferent electrode are effective, they tend to produce a ventricular complex of the opposite type.

The form of the complexes obtained by leading from points further to the left has, on the other hand, varied considerably. In branch block of the common type these complexes were sometimes of small amplitude, and showed no sharp deflections. Sometimes there was no deflection which could be regarded as a principal upstroke; when such a deflection could be recognized, it always occurred later than the chief upstroke of the earlier leads of the series, but it often rose so slowly as to make the evaluation of its significance difficult or impossible. It may have been in these cases that the exploring electrode was too far from the surface of the heart for our purpose, or that the investigation was not carried far enough to the left to enter the left ventricular field proper.

The three cases of bundle-branch block of the rare type which we have discussed are the only ones that we have had the opportunity of studying. It will be noted that although the chief upstrokes of the precordial leads taken from the left side of the precordium in this type of branch block are early in comparison with the chief upstrokes of leads from the right side of the precordium in the same subject, they are relatively late when compared with the earliest chief upstrokes obtained in branch block of the common type. This observation is consistent with the fact that the chief upstrokes obtained from the left side of the precordium are later than those obtained from the right side in cases in which the ventricular complex of the electrocardiogram is of the normal type. In most cases of bundle-branch block the heart is greatly hypertrophied. It cannot be assumed that the hypertrophy and the myocardial changes present are confined to the muscle of the homolateral ventricle. It is not surprising therefore that the earliest chief upstrokes obtained in cases of branch block are sometimes later than the chief upstrokes obtained by leading from the same part of the precordium in normal subjects.

When the complexes yielded by serial precordial leads in clinical bundle-branch block are compared with those obtained by serial semidirect leads in experimental canine branch block, it is clear that the common type of clinical branch block must be left branch block, not right, and that the rare type of clinical branch block must be right, not left. This conclusion is in harmony with the form of the complexes obtained by Barker, Macleod, and Alexander[9] by electric stimulation of the exposed human heart.

It is hoped that serial precordial leads may aid in the solution of other problems, such as the location of the conduction defect in various types of intraventricular block, the order of ventricular excitation in ventricular hypertrophy, and certain problems connected with the T-deflection, particularly those which relate to the location of the infarcted area in coronary thrombosis. We do not wish, however, to give the impression that the curves obtained by this method of leading are always easy to interpret. We have found, for instance, that ventricular extrasystoles of the type in which the most prominent deflection of the ventricular complex is downward in Lead I and upward in Lead III do not always yield, as might be expected, results similar to those obtained in the rare type of branch block. Except for bundle-branch block, however, too few cases of any one type have been examined to permit any definite conclusions to be drawn at this time.

SUMMARY

Leads in which one electrode (the exploring electrode) is placed close to the heart and the other (the indifferent electrode) at a distance from it are semidirect leads. In experiments on dogs serial semidirect leads were taken from the surface of a pad of gauze soaked in warm normal salt solution and laid upon the exposed heart. The galvanometer connections were made in such a way that relative negativity of the exploring electrode yielded an upward deflection in the completed curve.

In animals in which bundle-branch block had been produced, the chief upstroke of the ventricular complex occurred early in those semidirect leads in which the exploring electrode was close to the surface of the contralateral, and late in those leads in which this electrode was close to the surface of the homolateral ventricle. In the former case the mean potential of the exploring electrode during the QRS interval was usually negative; in the latter case, usually positive.

In precordial leads the exploring electrode is placed on the precordium and the indifferent electrode on the left leg.

Serial precordial leads in cases of clinical bundle-branch block of the common type yield results similar to those obtained by semidirect leads in experimental left branch block. In the rare type of bundle-branch block they yield results similar to those obtained in experimental right branch block.

The common type of bundle-branch block is left branch block; the rare type, right branch block.

The chief ventricular upstroke of semidirect leads, in which the exploring electrode is placed close to the ventricular surface, corresponds to the intrinsic deflection of direct leads from the ventricles in which a single contact is placed upon the muscle.

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THE TRANSVERSE DIAMETER OF THE HEART

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THE transverse diameter of the heart's shadow can be accurately measured by the x-ray and is both a satisfactory and a practical guide for estimating the size of the heart. The left auricle may enlarge without affecting the transverse diameter, but an increase in the size of any or all of the three remaining chambers will result in an increase in the measurement of this diameter. A definite decision as to whether or not a heart is enlarged can be made only if the transverse diameter is compared with some standard which will state what the diameter of the heart of an individual should be if that individual's heart were normal.

In 1919 Danzer[1] suggested the use of the cardiothoracic ratio as such a standard. According to this standard a heart is normal in size when its transverse diameter approximates one-half the internal diameter of the chest and is enlarged when its transverse diameter exceeds 50 per cent of the internal diameter of the chest. This theory is supported in papers by Jacobs and Worster[2] who also quote an affirmative opinion by Lee and Holmes, and by Martin.[3] None of these articles contains detailed data in support of the validity of this standard, and nowhere can one find a control study in which a group of normal individuals were examined. Smith and Blaedorn[4] hold a contrary opinion and contend that "any conclusion as to the relative size of the heart based on comparative dimensions, ratios or relations to body landmarks is fallacious and should be applied clinically with great reserve."

In 1926 Fred J. Hodges and J. A. E. Eyster[5] prepared a table for the prediction of the cardiac area and the transverse diameter in any normal adult male whose age, weight and height are known. The figures for the transverse diameter were derived from the formula $TD = +0.1094 \times A - 0.1941 \times H + 0.8179 \times W + 95.8625$, in which TD represents the transverse diameter, A the age, H the height and W the weight. The data were obtained from eighty subjects who showed no sign of cardiac abnormality. The measurements were made by orthodiagraphy. The authors concluded that if a heart is found to be 5 mm. wider in its greatest diameter as predicted by the formula the chances are three to one that the enlargement is pathological. A later article by Eyster[6] states that in one hundred more cases (no mention of sex) which have been added to the original series, 3 per cent exceeded the predicted transverse diameter by more than 10 per cent. A table based on the formula enables one to make a quick calculation of the predicted diameter for

any case and to dispense with the use of the formula which is too cumbersome and time consuming for ordinary clinical work. For the mathematical details the authors' papers should be consulted.

It must be emphasized that the table of Hodges and Eyster is applicable to measurements obtained by orthodiagraphy only and not to those obtained by teleroentgenography. The measurement of the transverse diameter in the teleroentgenogram is always greater than the actual width. This excess varies in different individuals, the divergence of the rays being influenced largely by two factors, the size of the heart and the distance that the heart lies from the anterior chest wall and therefore from the x-ray plate. Paul D. White in his recent volume on *Heart Disease* estimates that in the teleroentgenogram the error of excess for the transverse diameter is from 0.5 cm. to 1.5 cm. (4 per cent to 12 per cent) in normal hearts and in pathological hearts as much as 2.0 cm. In orthodiagraphy there are no such sources of error because only the direct central ray is used in outlining the heart.

The technic employed in the present study was as follows: The position of the central ray is determined and the site marked by a circular dot made with a black lead pencil. This is more convenient than a lead marker and is just as clearly seen. The patient breathing quietly stands in front of the screen, the black dot, i.e., the central ray is made to follow the outline of the heart and the tracing is recorded by means of a side arm which moves synchronously with the tube and the screen. It is important that the screen be moved only in the one vertical plane. Otherwise the central ray will change its position and nullify accurate results. For purpose of control the furthermost points on the left and right borders are again marked, and if they correspond with similar points on the tracing, one has reasonable assurance of the correctness of the findings. Occasionally an accurate record cannot be made because of the obscurity of the apex during quiet respiration. Deep inspiration may visualize such an apex, but it also lengthens the heart and narrows the transverse diameter, which make it inapplicable in this investigation.

In the present study the actual transverse diameters found in one hundred noncardiac males are compared with the predicted transverse diameters of Hodges and Eyster for these same individuals. The measurements of one-half the internal diameter of the chest also were obtained in ninety-seven of these one hundred cases and compared with the actual transverse diameters. The tabulations of these figures should enable one to test the validity of either standard and to compare the values of each.

Seventy-five women also were examined and their cardiac transverse diameters studied in a similar manner.

These 175 individuals comprise a successive number of ambulatory noncardiac patients who presented an opportunity for orthodiagraphic study. None showed any evidence of heart disease or any signs or symp-

TABLE I

NONCARDIAC MALES

NO.	AGE	WEIGHT KILOS	HEIGHT CM.	TRANSVERSE DIAMETER	PREDICTED DIAMETER OF HODGES & EYSTER	ONE-HALF INTERNAL DIAMETER OF CHEST
1	41	55	171	10.6	11.1	11.8
2	55	70	172	13.8	12.6	11.5
3	49	56	168	11.6	11.3	11.9
4	32	67	169	12.1	12.1	—
5	53	68	168	12.1	12.4	12.2
6	42	66	179	11.7	11.8	
7	61	65	168	10.9	12.1	12.7
8	43	79	178	13.9	13.0	13.2
9	36	87	183	14.1	13.5	14.5
10	43	76	174	12.3	12.8	12.5
11	29	98	187	13.4	14.2	13.0
12	58	84	166	14.1	13.7	12.0
13	19	61	168	10.6	11.5	
14	23	62	174	11.5	11.5	12.0
15	54	65	164	12.9	12.2	11.7
16	23	64	171	10.0	10.9	12.0
17	28	55	178	11.5	10.8	12.5
18	31	63	169	10.8	11.7	11.0
19	51	70	161	12.2	12.6	12.7
20	46	60	169	12.9	11.6	11.7
21	35	55	163	11.0	11.2	11.8
22	42	77	170	14.4	13.0	12.7
23	47	80	177	15.0	13.1	13.2
24	22	65	178	12.3	11.9	13.0
25	54	78	179	12.0	12.9	12.2
26	53	77	173	13.3	13.0	12.6
27	28	60	178	10.3	11.2	11.9
28	32	69	183	10.5	12.0	12.7
29	46	86	176	13.7	13.6	12.7
30	44	93	180	14.0	14.1	12.7
31	51	74	173	12.7	12.8	13.1
32	42	77	166	14.2	13.0	12.0
33	57	87	175	13.8	13.8	12.1
34	23	67	178	12.1	11.9	12.7
35	60	67	167	12.4	11.3	11.2
36	28	63	170	11.7	11.6	12.0
37	46	59	170	11.1	11.6	11.7
38	42	78	178	13.3	12.9	12.3
39	44	60	169	11.2	11.7	11.5
40	31	69	178	11.4	12.0	11.7
41	46	86	178	13.9	13.6	12.5
42	53	70	169	12.2	12.5	11.2
43	29	91	170	14.6	13.9	13.4
44	19	71	168	12.2	12.1	12.5
45	28	69	170	11.6	12.0	12.5
46	39	61	179	12.2	11.5	13.0
47	28	55	173	10.8	10.9	12.2
48	27	70	185	12.0	11.9	12.7
49	50	88	191	14.2	13.6	14.0
50	27	65	176	12.0	11.7	13.1
51	30	84	158	13.1	13.4	12.8
52	31	58	170	9.9	11.3	13.0
53	19	65	181	10.5	11.6	11.8
54	26	54	172	10.0	10.8	12.6
55	51	71	174	11.4	12.5	11.0

TABLE I (CONTINUED)

NONCARDIAC MALES

NO.	AGE	WEIGHT KILOS	HEIGHT CM.	TRANSVERSE DIAMETER	PREDICTED DIAMETER OF HODGES & EYSTER	ONE-HALF INTERNAL DIAMETER OF CHEST
601	28	62	165	11.3	11.6	11.7
602	18	55	179	11.4	10.9	12.5
56	22	56	176	10.4	11.0	13.0
57	29	64	179	10.2	11.5	12.6
58	33	60	173	11.3	11.4	12.0
59	18	64	175	11.8	11.5	12.0
60	19	62	184	10.5	11.2	11.7
61	43	74	165	13.4	12.8	12.0
62	30	72	178	11.2	12.3	13.3
63	31	77	172	13.0	12.8	13.0
64	33	90	179	13.2	13.7	12.5
65	18	60	183	10.8	11.0	12.9
66	23	67	173	12.0	11.9	13.0
67	21	72	175	10.8	12.2	12.1
68	41	59	168	11.6	11.5	11.6
69	31	72	181	12.7	12.2	11.8
70	43	66	170	11.9	12.1	11.0
71	58	66	180	12.1	12.0	12.7
72	48	70	181	12.0	12.2	12.7
73	30	61	167	10.9	11.6	11.5
74	35	55	162	11.1	11.2	11.7
75	44	63	181	11.1	11.4	12.8
76	21	71	178	11.2	12.1	12.3
77	35	91	168	13.5	14.0	12.8
78	30	70	176	12.3	12.2	12.7
79	29	80	183	12.2	12.2	13.0
80	33	76	178	11.0	12.6	11.8
81	17	50	165	9.8	10.5	10.8
82	41	80	174	13.4	13.1	13.0
83	60	56	168	11.9	11.4	11.0
84	34	74	180	11.9	12.5	13.6
85	34	78	173	13.1	12.9	12.3
86	37	55	168	12.4	11.1	11.7
87	26	81	177	12.3	13.0	13.1
88	46	70	171	12.7	12.4	12.6
89	45	75	163	13.1	12.9	11.1
90	19	58	171	10.6	11.1	11.7
91	47	49	156	11.0	10.9	11.7
92	25	73	179	12.9	12.6	12.6
93	49	70	175	12.4	12.3	12.2
94	50	94	171	15.5	14.5	13.0
254	24	59	179	10.6	11.0	12.5
256	60	88	176	13.3	13.8	12.2
257	41	67	166	12.5	12.2	12.5
260	25	86	174	13.3	13.4	11.8
Total	3671	6961	17345	1213.6	1221.5	1195.1
Average	36.71	69.61	173.45	12.13	12.21	12.32

toms referable to the heart. No case was excluded on account of the size of the heart alone, because it was thought that the exclusion of an apparently large or small heart would be unjustified in an investigation which is concerned principally with the size of the heart in normal

persons. The position of the heart, whether vertical or horizontal, was not given consideration because it was felt that these positions are not abnormal, but probably are to a large extent characteristic of an individual's physique.

TRANSVERSE DIAMETER OF THE MALE HEART

In Table I the detailed figures of one hundred male subjects are recorded, giving for each the age, the weight, the height, the transverse diameter found, the predicted transverse diameter of Hodges and Eyster and the measurement of one-half the internal diameter of the chest.

Table II is presented to show that this group of 100 cases is comparable with Hodges and Eyster's group of 80 cases.

TABLE II

		AGE	HEIGHT	WEIGHT	TD
Hodges & Eyster	80 cases—Averages	31.10	175.46	69.162	12.17
Present series	100 cases—Averages	36.71	173.45	69.61	12.13

Table III presents in round numbers a summary of the variations found in Table I. The cases are arranged in groups in accordance with the amount of the variation of the actual transverse diameter from the prediction figures of Hodges and Eyster and from the figures which represent one-half the internal diameter of the chest. For purposes of comparison the groups are bracketed.

TABLE III

VARIATION CM.	3.5	3.0	2.5	2.0	1.5	1.0	0.5	0	0.5	1.0	1.5	2.0	2.5	CM.
From prediction figures of Hodges and Eyster					1	8	15	30	3	28	9	5	1	
						24%			61%			15%		
From ½ internal diameter of chest	1	2	4	6	9	19		15	3	9	12	9	4	4
				42%				27.5%			30%			

Explanation of Table III: zero represents the standard and the figures beneath it the number of hearts which had exactly the same transverse diameter as that estimated by the standards. The figures to the right of zero represent the distances in centimeters above the standard and the figures to the left similar distances below the standards. The number of hearts which showed any variation are tabulated in accordance with the amount of the variation, e.g., in twenty-eight hearts the actual transverse diameter exceeded the predicted diameter by 0.5 cm. or less, in nine the excess was between 0.5 cm. and 1.0 cm., in five between 1.0 cm.

TABLE IV

NONCARDIAC FEMALES

NUMBER	AGE	WEIGHT KILOS.	HEIGHT CM.	TRANSVERSE DIAMETER	HODGES & EYSTER PREDICTED FIGURES FOR MALES	PREDICTED FIGURES ADJUSTED FOR FEMALES; MALE FIGURE MINUS 0.8 CM.	ONE-HALF INTERNAL DIAMETER OF CHEST
95	23	37	146	9.9	9.9	9.1	10.1
96	68	59	167	11.6	11.6	10.8	10.1
97	44	42	146	9.2	10.7	9.9	11.1
98	47	52	163	10.1	11.0	10.2	10.2
99	17	46	157	9.1	10.3	9.5	9.8
100	28	52	158	9.8	10.6	9.8	11.1
101	23	62	162	10.5	11.7	10.9	11.0
102	18	51	166	9.3	10.6	9.8	12.0
103	31	56	158	11.5	11.4	10.6	11.1
104	27	45	157	9.9	10.3	9.6	10.7
105	30	79	165	11.2	12.9	12.1	11.6
106	33	57	155	10.4	11.2	10.4	10.0
107	39	77	163	12.6	13.0	12.2	11.5
108	31	64	147	11.5	12.2	11.4	10.7
109	24	47	164	9.7	10.0	9.2	10.6
110	30	62	163	10.7	11.7	10.9	10.5
111	31	44	165	9.1	10.2	9.4	11.2
112	42	58	159	10.9	11.6	10.8	10.6
113	37	45	151	9.1	10.7	9.9	10.2
114	22	46	168	9.7	10.1	9.3	12.0
115	36	65	163	10.0	12.0	11.2	10.9
116	16	58	170	10.5	11.1	10.3	11.8
117	28	56	163	10.8	11.2	10.4	11.0
118	24	48	164	9.4	10.4	9.6	11.5
119	22	48	163	10.5	10.4	9.6	11.5
120	33	57	152	9.8	11.6	10.8	11.0
121	50	67	159	11.8	12.5	11.7	10.8
122	27	63	173	10.3	11.6	10.8	11.1
123	35	52	160	9.4	11.0	10.2	11.5
124	24	55	165	10.2	11.1	10.3	11.5
125	26	60	164	11.6	11.5	10.7	12.1
126	36	74	162	11.5	12.8	12.0	11.2
127	36	54	163	10.6	11.1	10.3	—
128	40	63	159	10.8	12.0	11.2	—
129	24	77	165	12.4	12.9	12.1	11.6
130	32	68	159	11.2	12.3	11.5	12.0
230	34	63	161	11.3	11.9	11.1	10.5
132	27	83	168	10.7	13.3	12.5	10.2
133	33	73	162	11.4	12.7	11.9	11.6
134	41	61	163	11.4	11.7	10.9	11.1

TABLE IV (CONTINUED)

NONCARDIAC FEMALES

NUMBER	AGE	WEIGHT KILOS.	HEIGHT CM.	TRANSVERSE DIAMETER	HODGES & EYSTER PREDICTED FIGURES FOR MALES	PREDICTED FIGURES ADJUSTED FOR FEMALES; MALE FIGURE MINUS 0.8 CM.	ONE-HALF INTERNAL DIAMETER OF CHEST
135	19	46	164	9.6	11.1	10.3	11.7
136	23	52	163	9.1	10.8	10.0	10.7
137	40	58	166	10.5	11.5	10.7	11.0
138	71	63	161	11.8	12.1	11.3	11.5
139	22	51	166	10.3	10.7	9.9	10.7
140	38	61	168	11.3	11.6	10.8	11.5
141	26	46	155	10.4	10.7	9.9	10.2
142	26	78	169	12.5	12.9	12.1	11.5
143	33	65	160	10.5	12.1	11.3	11.2
144	20	48	164	10.2	10.5	9.7	10.9
145	26	56	173	9.3	11.0	10.2	11.1
146	36	75	161	11.4	12.9	12.1	11.0
147	32	59	169	9.3	11.4	10.6	11.5
148	31	74	166	12.1	12.7	11.9	11.5
150	18	52	155	10.9	10.9	10.1	10.2
151	18	48	154	9.8	10.6	9.8	11.0
152	25	80	166	13.3	13.1	12.3	11.8
153	31	79	165	12.3	13.1	12.3	10.8
154	19	57	164	9.7	11.1	10.3	11.2
155	40	67	174	12.0	12.1	11.3	11.5
156	22	61	168	9.6	11.5	10.7	11.0
157	28	58	161	11.2	11.4	10.6	10.6
158	25	61	159	10.8	11.6	10.8	11.5
159	31	77	169	12.7	12.9	12.1	11.8
160	58	67	161	12.4	12.4	11.6	10.5
161	28	70	164	10.4	12.3	11.5	11.6
162	18	56	162	9.8	11.1	10.3	11.0
163	19	49	156	10.4	10.7	9.9	10.7
164	21	62	162	12.0	11.7	10.9	11.7
165	55	63	161	11.5	12.1	11.3	11.7
166	36	63	161	9.7	11.9	11.1	10.0
167	26	54	170	10.8	10.9	10.1	11.7
168	19	58	160	10.5	11.3	10.5	10.5
169	26	53	153	9.7	10.6	9.8	9.5
Total	2297	4453	12153	800.2	862.5	802.5	802.2
Average	30.62	59.37	162	10.67	11.50	10.70	11.01

and 1.5 cm., and in one between 1.5 cm. and 2.0 cm. To the left of zero, hearts with transverse diameters smaller than the prediction figures are recorded in the same manner. Variations from the standard where one-half the internal diameter of the chest is used are similarly recorded.

In this series of one hundred male subjects the transverse diameter of the heart was found to be within 0.5 cm. of the predicted figures in 61 per cent. Only 27 per cent fell within 0.5 cm. of the measurement of one-half the internal diameter of the chest.

In the group in which the question of enlargement arises, those hearts which are wider than the standard by more than 0.5 cm., 15 per cent of these supposedly normal hearts would be considered enlarged according to the prediction figures and 30 per cent when one-half the internal diameter is used as a standard.

Twenty-four per cent of the hearts are small, i.e., the transverse diameter is less than the standard of Hodges and Eyster by more than 0.5 cm. In a corresponding bracket for one-half the internal diameter the figure is 42 per cent.

This table presents a comparison showing that the transverse diameter found approximates the predicted figures of Hodges and Eyster in a far greater percentage than it does the measurement of one-half the internal diameter of the chest. In fact the latter measurement is found to vary from the actual diameter in such a large percentage of cases that it is of questionable value as a standard in estimating abnormality in the size of a heart.

TRANSVERSE DIAMETER OF THE FEMALE HEART

The prediction table of Hodges and Eyster was prepared from data obtained in the examination of male subjects only. Table IV shows that this standard is not applicable to this group of 75 women. However, by reducing the predicted transverse diameter for men by 0.8 cm. a standard for women is obtained. By the use of this adjusted standard it was found that the actual transverse diameter in the female varied from the adjusted prediction figures to a degree which is practically the same as the results obtained in the examination of the male subjects.

A comparison of the variations in the male and female groups is seen in Table V.

TABLE V

VARIATION	2.0	1.5	1.0	0.5	0	0.5	1.0	1.5	2.0	CM.
From prediction figures of 100 males	1	8	15	30	3	28	9	5	1	
		24%			61%			15%		
From suggested female standard (75 cases)	1	5	11	16	6	23	12	1		
		22.7%			60%			17.3%		

It is evident from Table V that in this group of 75 female subjects the transverse diameter of the heart is smaller by 0.8 cm. than the transverse diameter in a male subject of the same age, weight and height.

Table VI which is arranged in the same way as Tables III and V shows that as in the male group, the measurement of one-half the internal diameter of the chest varies from the actual transverse diameter in such a large percentage of cases that it cannot be used as a satisfactory guide in judging abnormalities of the size of the female heart.

TABLE VI

VARIATION IN FEMALES CM.	3.0	2.5	2.0	1.5	1.0	0.5	0	0.5	1.0	1.5	2.0
From adjusted prediction figures			1	5	11	16	6	23	12	1	
				22.7%			60%			17.3%	
From one-half internal diameter	1	6	2	10	11	13	1	14	10	4	1
			41%				38.5%			20.5%	

COMBINED GROUPS: MALE AND FEMALE

Using the prediction table of Hodges and Eyster for males and the adjusted prediction figures for females Table VII shows the amount of variation from the standards for these 175 individuals in whom there was no reason for suspecting heart disease.

TABLE VII

VARIATION CM.	2.0	1.5	1.0	0.5	0	0.5	1.0	1.5	2.0
175 cases	2	13	26	46	9	51	21	6	1
		23.5%			60.5%			16%	
			87%						

It is seen from Table VII that the actual transverse diameter of the heart in 175 cases was found to be within 0.5 cm. of the predicted diameter in 60.5 per cent of the cases, and within 1.0 cm. in 87 per cent. It was found larger by more than 0.5 cm. in 16 per cent and smaller by more than 0.5 cm. in 23.5 per cent. In this group which varies from the predicted figures by more than 0.5 cm. seven hearts, or 4 per cent of the total, were larger by more than 1.0 cm.; and fifteen hearts, or 8.5 per cent, were smaller by the same margin. If these findings are supported by further studies, it is suggested that a heart found to be within 0.5 cm. of the predicted figures be considered normal in size. Expressed in another way the average range in size of the transverse diameter of the normal heart is within 0.5 cm. of the predicted figures.

The twenty-eight hearts, or 16 per cent, which are larger by more than 0.5 cm. offer an opportunity for some speculation. Twenty-one hearts

(12 per cent) are larger than the standard by more than 0.5 cm., but by less than 1.0 cm. Whether or not they should be considered enlarged is a question which should remain open for the present. The seven hearts (4 per cent) which are greater by more than 1.0 cm. in their transverse diameter probably should be considered definitely enlarged. Whether or not they are pathologically enlarged is uncertain, because, as previously stated, we have been studying only the transverse diameter of hearts which otherwise showed no abnormality and have excluded none because of size alone. It is suggested, however, that enlargement of the degree found in these seven subjects even in the absence of other signs is a definite enough abnormality to justify the diagnosis of "possible heart disease."[7]

COMMENT

It is doubtful whether a more exact standard can be devised for estimating clinically the diameter of the human heart, which necessarily varies in size and capacity under physiological conditions. Hodges and Eyster, however, suggest that greater accuracy might be obtained by employing another variable in addition to age, weight and height. If so it might be possible to reduce the percentages of hearts smaller by more than 0.5 cm., 24 per cent for males and 22.7 per cent for females, to still lower figures. But even here the variation is not pronounced, as only 9 per cent of the male and 8 per cent of the female hearts are smaller by more than 1.0 cm.

It is worthy of note in considering the margin of error in the practical application of the prediction figures of Hodges and Eyster that in this series of 175 noncardiac individuals the actual transverse diameter varies from the standard (using the adjusted standard for females) by more than 1.0 cm. in only 13 per cent, 4 per cent being larger and 9 per cent smaller.

The tables represent data obtained by orthodiagraphy and therefore are not applicable to the measurements by teleroentgenography. The articles previously referred to in this paper deal with the use of the cardiothoracic ratio in the teleroentgenogram only and not in the orthodiagram. The literature contains no study of the application of this ratio to the orthodiagram. Nevertheless it has been used quite frequently in estimating variation in the heart's size as measured by orthodiagraphy.

If, as the present study indicates, the cardiothoracic ratio is not applicable to orthodiagraphic measurements, which are exact, it is somewhat difficult to understand how this ratio can be an index of size in the teleroentgenogram where there are certain inherent errors which vary with each individual patient.

These same errors will make it difficult to adjust the standard of Hodges and Eyster so that it may be applied to the measurements obtained in teleroentgenography.

CONCLUSIONS

The prediction table of Hodges and Eyster is a fairly satisfactory guide in enabling an examiner to judge abnormality in the size of the male heart and to estimate the degree of enlargement.

The adjusted standard for females in which the figures for males is reduced by 0.8 cm. is equally satisfactory.

One-half the internal diameter of the chest in the orthodiagram is a measurement which does not approximate the actual transverse diameter of the normal heart often enough to have much value as a standard guide.

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THE DIURETIC EFFECT OF DIGITALIS*

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WILLIAM WITHERING[27] in his original communication concerning the action of digitalis chiefly stressed the diuretic action of the drug. It is true he stated "it has a power over the motion of the heart to a degree yet unobserved in any other medicine and this power may be converted to salutary ends" but the main emphasis has to do with "a new diuretic which though not infallible" he believed to be "much more certain than any in present use" and "that it will often produce this effect after every other probable medicine has been fruitlessly tried." However, there has not been unanimous agreement with this observation of the excellent diuretic effect of digitalis. Germain[10] and Winogradoff[26] denied that digitalis possesses diuretic properties, and stated that the diuresis which often follows when an amelioration of the condition of the circulation has been produced by it in organic disease of the heart is only a mediate effect resulting from a return of the circulation to its normal condition. Among those who observed the diuretic effect of digitalis may be mentioned Christian,[5] Andrall and Christian and Lemaitre, and Brunton.[4] Brunton, in experiments on himself and other human subjects, concluded that digitalis acts as a diuretic in anasarca, especially if the anasarca is caused by heart disease, and that it sometimes, but not always, acts as such even in health. This observer further stated, "when digitalis acts upon the normal man so as to produce diuresis, the drain of fluid becomes so great, as I have found in my experiments, the thirst it induces becomes intolerable." Joerg[14] who carried out experiments on several healthy men, women, and children, found the output of urine increased with only one exception. Stadion,[22] after putting himself on a diet of weighed food and after determining the normal amount of his urine, took digitalin for eighteen days, beginning with 2 mg., and daily increasing the dose by 1 mg. At the conclusion of the experiment his urine had diminished in quantity.

Peculiarly little notice was paid to the original work of Withering for more than one hundred years, although in this period there were such outstanding teachers of conditions of the heart as Hope, Stokes, and Austin Flint. Physicians relied on other diuretics than digitalis to combat the edema of cardiac failure. MacKenzie[18] was the first

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clinician to demonstrate conclusively the correctness of Withering's observations and instructions regarding the uses and administration of digitalis. Since MacKenzie's contributions, there has accumulated a vast literature on digitalis and much has been written about its effect.

One is impressed with the amount of study of this drug, and with the relatively few carefully controlled and standardized studies both of the healthy human subject and of patients with cardiac failure and edema. Few investigations have fulfilled the essential requirements of a preliminary period of control for the healthy human subject, or for patients with cardiac failure, of a preliminary period of absolute bodily rest; a constant diet of weighed food of known low water and low mineral content; daily extra intake of fluid of constant and carefully measured amount, and daily estimation of the output of urine, of body weight, of pulse rate, of blood pressure and of symptoms of the effect of digitalis.

However, there have appeared several excellent studies of the diuretic effect of digitalis in cases of myocardial failure with congestion and edema. Examples of such contributions are those of Cohn,[6] West and Pratt,[23] and Pratt[20] Eggleston,[8] Fraser,[9] Jensen,[13] Luten,[17] Christian,[5] Marvin[19] and Hay, Jones and Ince.[11] There is general agreement among these workers that when edema is present, either apparent or masked, it is usual for definite diuresis to occur under the influence of digitalis. If, however, edema is absent, they find no diuretic effect. This diuretic effect, in cases of heart failure and edema, they believe depends chiefly on the action of digitalis on the heart muscle alone. They further assumed that the fall in urinary output toward the end of treatment is due to diminished intake of fluid, associated with nausea and anorexia resulting from toxic symptoms of the drug. The diuretic effect was observed in cases with normal cardiac rhythm, as well as in cases with fibrillation of the auricles. It has also been shown that in establishing a sufficient basis for the study of such diuretic effect one must take into consideration the presence or absence of hypertension, the etiologic classification of heart disease, the stage of heart failure, and the dosage, potency, and rapidity of administration of the drug.

In treating cases of cardiac failure with considerable edema, Bannick, N. M. Keith and I not infrequently noted failure to produce satisfactory diuresis with digitalis. In such cases we were frequently able to obtain excellent diuresis by employing other diuretics. Willius[24] has reported a similar experience with other diuretics. Because of this experience the present work was attempted to determine the diuretic effect of digitalis both on the healthy human subject and in cases of heart failure with edema.

TABLE I

DIETS USED IN THESE EXPERIMENTS

SUBJECT OR PATIENT	DIAGNOSIS	AGE, YEARS, SEX	1931	CARBOHYDRATES, GM.	PROTEINS, GM.	FAT, GM.	TOTAL CALORIES	WATER, C.C.	SODIUM CHLORIDE, GM.
DIET FOR NORMAL SUBJECTS									
Subject 1 (experiment 1)	Normal subject	32 M		230	60	88	2000	820	1.5
Subject 1 (experiment 2)	Normal subject	32 M	10/27 to 31	160	60	106	1800	1180	3.3
			11/ 1 to 7	152	59	79	1500	1150	3.0
Subject 1 (experiment 3)	Normal subject	32 M		124 to 164	56 to 59	62 to 90	1320 to 1495	860	1.4
Subject 2	Normal subject	31 M		230	60	88	2000	820	1.5
Subject 3	Normal subject	26 M		230	60	88	2000	820	1.5

TABLE I (CONTINUED)

SUBJECT OR PATIENT	DIAGNOSIS	AGE, YEARS, SEX	1931	CARBOHYDRATES, GM.	PROTEINS, GM.	FAT, GM.	TOTAL CALORIES	WATER, C.C.	SODIUM CHLORIDE, GM.
DIETS FOR PATIENTS WITH MYOCARDIAL FAILURE									
Patient 1	Rheumatic mitral endocarditis with stenosis	34 F	4/ 5 to 17	168 to 231	32 to 40	71 to 92	1440 to 2000	640 to 830	1.0
(first admission)			4/18 to 20	200 to 222	46 to 49	111 to 123	2000 to 2200	760 to 820	1.1
(second admission)				200 to 243	27 to 40	73 to 86	1740 to 1900	760 to 830	1.0
2	Arteriosclerosis; essential hypertension	45 M	4/ 5 to 12	123 to 133	40	54	1175 to 1220	775 to 810	1.2
			4/18 to 20	243	40	92	2000	835	1.3
3	Questionable coronary sclerosis; adenoma of thyroid gland	59 F		76 to 122	25 to 39	35 to 54	720 to 1175	445 to 765	1.1
4*	Rheumatic mitral endocarditis with stenosis; subacute arthritis	39 F		240	40	97	2000	1100	3.4
5	Arteriosclerosis; coronary sclerosis	58 M		85 to 133	23 to 40	30 to 54	745 to 1220	545 to 810	1.1
6	Arteriosclerosis	72 F		62 to 116	36 to 38	41 to 54	840 to 1100	400 to 700	1.1
7	Arteriosclerosis; essential hypertension	47 F		97 to 148	32 to 40	57 to 80	1030 to 1500	610 to 790	1.2
8	Arteriosclerosis	67 M		87 to 133	23 to 40	43 to 54	870 to 1220	425 to 810	1.0
9	Rheumatic mitral endocarditis; auricular fibrillation	25 M		76 to 148	33 to 40	71 to 80	1075 to 1500	700 to 810	1.2
10	Arteriosclerosis; hypertension	46 M		105 to 135	26 to 40	47 to 54	1050 to 1200	605 to 810	1.2
11	Arteriosclerosis; severe hypertension	57 F		103 to 133	37 to 40	46 to 54	1080 to 1200	650 to 810	1.1
12	Arteriosclerosis; essential hypertension; aortic stenosis	45 M	5/26 to 6/5	121 to 133	38 to 40	46 to 54	1050 to 1220	690 to 810	1.2
			6/ 6 to 7	243	40	92	2000	810	1.2

*This diet was not weighed, but was carefully estimated daily.

METHOD OF STUDY

The diuretic effect of digitalis was studied on three healthy human subjects, and on twelve patients with congestive heart failure and considerable edema. One patient was observed and treated on two different occasions. None of the patients exhibited evidence of serious impairment of renal function. The study was made on one of the healthy human subjects three times, varying the diet and doses of digitalis with each experiment. To insure standard experimental conditions, all the subjects were given a diet of weighed food, as constant as possible from day to day, of known low salt, water and protein content, the same as that employed by Keith, Smith and Whelan.[16] The weighed food both of the healthy subjects and of those with myocardial failure is shown in Table I. The total caloric values of the diet given to normal, healthy subjects were adequate, but the food given to patients with cardiac failure was low in total calories. This food was given to the patients with cardiac failure because they were at constant rest in bed, which reduced their caloric requirements, and because it was essential that all food should be eaten. The content of sodium chloride was low in all of the diets with two exceptions, and varied between 1 and 1.5 gm. daily. The diets of patient 4 and healthy subject 1, experiment 2, contained approximately twice the amount of sodium chloride that was present in the others. Attention is also called to the low water content of all the diets except that of healthy subject 1, experiment 2, and that of patient 4, which contained approximately 300 c.c. of water in excess of the others. The importance of the diet of weighed food, which was kept as constant as possible, is emphasized because there have been relatively few standardized experimental studies of digitalis in which such a diet has been employed. It is obvious that a study in which this factor is as carefully controlled as possible is of more significance and is more dependable than one in which this factor is ignored. Daily estimations were made of body weight, pulse rate, blood pressure and total output of urine in twenty-four hours. The intake of extra fluid was as constant as possible with each subject, and was carefully estimated, varying from 800 to 1,000 c.c. daily with the different subjects. A preliminary period of absolute bodily rest, with no medication other than the necessary sedatives, was given the patients who had congestive failure; the healthy subjects also had a preliminary period of control without medication. At the conclusion of the periods of control a standardized preparation of powdered leaf of digitalis was given to each subject in adequate amount.* Electrocardiograms were taken daily of healthy subjects, and every three to four days in the cases of heart failure. Careful observation was made of all the subjects for clinical objective

*Burroughs Wellcome tablets containing the powdered leaf were used.

and subjective signs of digitalis effect. The output of urine for twenty-four hours was submitted daily to estimation of the total chloride, the total fixed base, and the total nitrogen content.*

RESULTS IN HEALTHY HUMAN SUBJECTS

Fig. 1 shows graphically the digitalis effect in a healthy human being (subject 1) using adequate doses of digitalis in three different experiments. The daily intake of extra fluid was constant for each experiment, and was 800 c.c. in the first two experiments and 1,000 c.c. in the third experiment. The weighed diet contained 60 gm. of

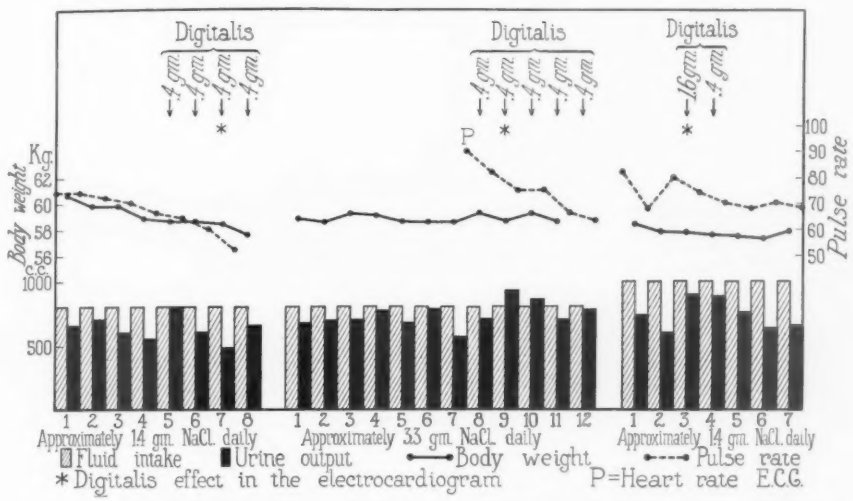

Fig. 1.—Digitalis effect on normal subject in three experiments. The effect varies when the amount of water and salt of the diet is varied. Intake of fluid does not include fluid in food.

protein, 1,500 to 2,000 calories, and was low in water and salt. The daily content of water of this diet was 820 c.c. in the first experiment, 860 c.c. in the third experiment, and 1,150 to 1,180 c.c. in the second experiment. The salt content of the diet during the second experiment, as is shown in Table I, was approximately twice that of the first and third experiments; the dietary fluid content in the second experiment was approximately 300 c.c. more than that of the first and third experiments.

Characteristic electrocardiographic evidence of digitalis effect was observed in all three of the experiments on this subject as well as on one of the other subjects (subject 2). The evidence consisted of a change in the T-wave, a prolongation of the conduction time, or both.

There was only slight diuresis in the first experiment; the output of urine rose to 800 c.c. on the first day after administration of digitalis

*The chloride in the urine was determined by the method of Wilson and Ball. The determination of the total fixed base was by the method of Stadie and Ross. The total nitrogen was determined by the standard method of Kjeldahl.

TABLE II

CHEMICAL STUDIES OF SUBJECT 1, EXPERIMENT 3

FEBRUARY, 1931	WT., KG.†	URINE									DIGITALIS GM.	BLOOD*		
		VOLUME, C.C.	SPECIFIC GRAVITY	P_H	SODIUM CHLORIDE, GM.		FIXED BASE C.C. TENTH NORMAL		TOTAL NITROGEN, GM.			UREA MG. IN EACH 100 C.C.	PLASMA CARBON DIOXIDE COMBINING POWER, PER CENT	PLASMA CHLORIDE, MG. IN EACH 100 C.C.
					IN EACH 100 C.C.	IN ENTIRE SPECIMEN	IN EACH 100 C.C	IN ENTIRE SPECIMEN	IN EACH 100 C.C.	IN ENTIRE SPECIMEN				
19 to 20	58.3	660	1.015	5.4	0.24	1.58	94	620	0.87	5.74				
20 to 21	58.3	740	1.009	7.0	0.12	0.89	74	548	0.48	3.55				
21 to 22	57.7	630	1.023	5.6	0.25	1.58	151	951	1.34	8.44		34	65	617
22 to 23	57.5	900	1.016	5.8	0.21	1.89	99	891	0.92	8.28	1.6§	34	63	583
23 to 24‡	57.5	850	1.013	6.0	0.21	1.79	88	748	0.53	4.51	0.4§	28	64	608
24 to 25	57.3	740	1.013	5.8	0.15	1.11	77	570	0.63	4.66				
25 to 26	57.7	650	1.015	6.8	0.19	1.24	116	754	0.60	3.90		38	62	581
26 to 27	57.7	670	1.012	7.0	0.11	0.74	85	569	0.49	3.28		40	64	561
27 to 28	58.0	720	1.007	7.2	0.07	0.50	68	490	0.38	2.74				

*Blood withdrawn at 8 A.M. at end of twenty-four hours.
†Weighed at 8 A.M. at end of period of twenty-four hours.
‡Protein, 43 gm.; 1110 calories; water, 685 c.c.; approximately 1 gm. sodium chloride; extra water, 1000 c.c.
§February 22, digitalis, 0.4 gm, at 8 A.M., 2 P.M., 8 P.M.; February 23, digitalis 0.4 gm. at 2 A.M., 0.2 gm. at 8A.M. and 2 P.M.

and thereafter quickly dropped to a level generally below that of the control period. This result indicates that the diuretic effect was negligible. However, in the second experiment is slight but definite evidence of diuresis beginning on the second day of administration of digitalis. The slight but definite increase of the amount of sodium chloride and water in the diet might be a possible factor. In the third experiment, also, there was slight diuresis for two days after administration of digitalis. The rapid method of digitalization of Eggleston was employed during this experiment. Attention is directed to the daily intake of extra fluid, amounting to 1,000 c.c. during this experiment. This was 200 c.c. more than that during the first or second experiment. The daily output of urine during the third experiment never equalled or exceeded the daily intake of extra fluid.

The results of chemical studies of the healthy human subject in experiment 3 are shown in Table II. The output of urine for twenty-four hours was examined for its content of sodium chloride, total base, and total nitrogen; the whole blood for urea, and the blood plasma for carbon dioxide combining power and chloride. There was no increase in the daily concentration of chloride of the urine after administration of digitalis in this experiment. Similar studies, in experiment 1, also failed to give evidence of increase of the concentration of chloride after ingestion of adequate doses of digitalis. There was, however, a slight increase of the concentration of chloride in the urine in the second experiment, following the use of digitalis. Attention is again directed to the fact that the intake of chloride was greater in experiment 2. Excretion of nitrogen during the first few days (Table II) was somewhat irregular, but it averaged about 5 gm. daily. On the first day, after digitalis had been taken, there was a marked in-

TABLE III

DIURETIC EFFECT OF DIGITALIS ON SUBJECT 2

JULY, 1930	WEIGHT, KG.*	URINE									
		VOLUME, C.C.	P_H	SODIUM CHLORIDE, GM.		TOTAL NITROGEN, GM.		FIXED BASE, C.C. TENTH NORMAL		DIGITALIS, GM.
				IN EACH 100 C.C.	IN ENTIRE SPECIMEN	IN EACH 100 C.C.	IN ENTIRE SPECIMEN	IN EACH 100 C.C.	IN ENTIRE SPECIMEN	
28 to 29	58.8	550	5.6	0.52	2.86	1.29	7.10	166	913	
29 to 30	58.3	450	5.6	0.49	2.20	1.58	7.10	183	823	
30 to 31	58.3	500	5.8	0.29	1.45	1.77	8.85	157	785	
31 to August 1	57.6	400	6.0	0.24	0.96	2.07	8.30	176	705	
1 to 2	56.3	500	5.6	0.26	1.30	1.68	8.40	167	835	0.4†
2 to 3	54.4	440	5.6	0.29	1.27	1.86	8.18	165	725	0.4†
3 to 4	53.7	500	5.6	0.32	1.60	1.63	8.15	161	805	0.4†
4 to 5	52.6	475	5.6	0.26	1.23	2.30	10.92	154	732	0.4†

*Weighed at end of twenty-four hours.
†Digitalis, 0.4 gm., ingested once daily at 8:30 A.M.

crease in excretion of nitrogen, but a decrease in the next two days. Excretion of nitrogen during the last three control days after administration of digitalis was fairly constant, and averaged about 3 gm. daily.

Fig. 2 represents the digitalis effect in healthy human subject 2, who was likewise studied under carefully standardized conditions. Again, digitalis had no diuretic effect. Chemical studies of the same healthy person (subject 2) before and after administration of digitalis are shown in Table III. The concentration of chloride in the urine was not distinctly increased after the use of digitalis. Excretion of nitrogen during the first few days averaged 7.84 gm. daily. While the

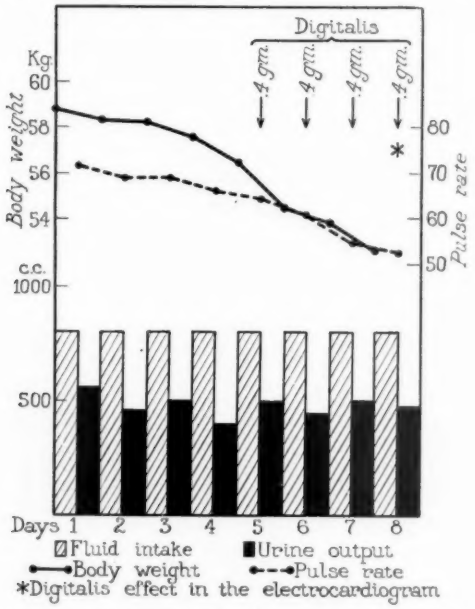

Fig. 2.—Effect of digitalis on normal subject 2. The intake of fluid does not include fluid in food.

subject was taking digitalis, excretion of nitrogen was constant for the first three days and was about the same in quantity as during the control period, averaging 8.24 gm. daily. There was an increase of excretion of nitrogen, however, on the fourth day of administration of digitalis; the total excretion on this day was 10.92 gm. The total excretion of fixed base gradually diminished daily during the control period of four days, and averaged 806 c.c. of tenth normal base daily. During and following administration of digitalis, excretion of total fixed base but was little changed, averaging 774 c.c. tenth normal base daily. Healthy human subject 3 gave evidence of no diuretic effect following adequate doses of digitalis.

Table IV contains a brief outline of the digitalis effect in all of the experiments on the healthy human subjects. Definite slowing of the

TABLE IV

SUMMARY OF ACTION OF DIGITALIS ON HEALTHY SUBJECTS

	CONTROL PERIOD							PERIOD OF DIGITALIS EFFECT								
					ELECTROCARDIOGRAM							ELECTROCARDIOGRAM				
SUBJECT	PULSE, BEATS EACH MINUTE	AVERAGE DAILY OUTPUT OF URINE, C.C.	LOSS OF WEIGHT, KG.	SODIUM CHLORIDE IN URINE, GM. IN EACH 100 C.C.	CARDIAC RATE	RHYTHM	T-WAVE (LEAD III)	PULSE, BEATS EACH MINUTE*	AVERAGE DAILY OUTPUT OF URINE, C.C.	LOSS OF WEIGHT, KG.	SODIUM CHLORIDE IN URINE, GM. IN EACH 100 C.C.	CARDIAC RATE	RHYTHM	T-WAVE LEAD II	T-WAVE LEAD III	DIGITALIS, GM.
1 (experiment 1)	74	625	1.9	0.22	86	Sinus regular	Inverted	53	635	1.1	0.10	56	Sinus irregular	Diphasic	Inverted	1.6 in four days
1 (experiment 2)		700	0.3	0.47	90	Sinus regular	Inverted		790	0	0.63	56 to 72	Sinus irregular	Inverted	Inverted	2.0 in five days
1 (experiment 3)	88	677	0.6	0.20	93	Sinus regular	Inverted	68	755	0	0.15	68	Sinus regular	Inverted	Inverted	2.0 in 48 hours
2 (experiment 4)	71	475	0.9	0.39	60	Sinus regular	?	58	478	3.7	0.28	51	Sinus irregular	?	Inverted	1.6 in four days
3 (experiment 5)	66	637	0	0.12	72	Sinus irregular; ventricular premature contraction	?	58	562	0.9	0.09	67	Sinus irregular	?	Unknown	1.6 in four days

*Pulse rate taken when patient was under basal metabolic conditions at 7:30 A.M.

cardiac rate was noted in all following administration of digitalis. Characteristic electrocardiographic evidence of digitalis effect was also observed in four of the five experiments. The blood pressure remained normal throughout. The diuretic effect of digitalis was negligible in the first experiment (subject 1), definite in the second experiment (subject 1), slight for two days in the third experiment (subject 1), absent in the fourth experiment (subject 2) and also absent in the fifth experiment (subject 3). Thus of the five experiments the diuretic effect was absent in three, was slight in one, and was definite in only one. The average concentration of sodium chloride in the urine was increased in one experiment after ingestion of digitalis, and was not increased in any of the remaining four experiments.

TABLE V

ACTION OF DIGITALIS IN MYOCARDIAL FAILURE WITH DIURESIS (PATIENT 4)

JUNE, 1930	WEIGHT, KG.	PULSE, BEATS EACH MINUTE	URINE VOLUME C.C.	SODIUM CHLORIDE		DIGITALIS, GM.
				GM. IN EACH 100 C.C.	GM. IN ENTIRE SPECIMEN	
8	62.3	90	1000	0.43	4.30	
9	62.3	88	825	0.48	4.00	
10	61.6	88	700	0.49	3.40	
11	61.1	80	800	0.52	4.10	
12	61.4	82	600	0.48	2.90	
13	61.1	86	600	0.45	2.70	0.3
14	61.4	86	500	0.16	0.80	0.2
15	60.5	68	850	0.16	1.40	0.3
16	60.7	64	1025	0.36	3.70	0.3
17	60.8	74	1375	0.36	4.95	0.3
18	61.0	80	950	0.31	2.95	0.3
19	59.5	76	1150	0.31	3.56	
20	59.5	74	525	0.22	1.16	
21	60.0	86	500	0.21	1.05	
22	58.3	84	650	0.18	1.17	

RESULTS IN CASES OF CARDIAC FAILURE AND DEPENDENT EDEMA

In all of the twelve cases of cardiac failure there was definite dependent edema in addition to the other usual signs of failure of the circulation. None of the patients exhibited evidence of serious impairment of renal function; none had a positive Wassermann reaction. In one case only there was fibrillation of the auricles. Two patients had coronary sclerosis; three had rheumatic endocarditis, and several, arteriosclerotic and hypertensive myocardial disease. Before the present study, five patients had not experienced any previous break in compensation; five had had one previous break in compensation; one patient had had two previous periods of decompensation, and one had had three periods of decompensation.

All the patients had a preliminary period of bodily rest, without medication other than the necessary sedatives. This preliminary period of rest was often of longer duration than the figures show,

owing to the fact that the charted days were only those when the patient was receiving a constant diet of weighed food. Some of the preliminary days, when the patient received salt-free, unweighed food are not shown.

Patient 4 experienced definite and sustained diuresis, beginning on the third day of administration of digitalis. The diuresis was accompanied by definite decrease in pulse rate, definite loss of weight, and marked improvement in clinical symptoms. Table V is a brief recapitulation of this case. While the diuretic response was satisfactory, the daily average output was only slightly increased over the control period (Table VIII). Despite definite diuresis, the concentration of chloride in each 100 c.c. of urine is not increased, indicating that when

TABLE VI

ACTION OF DIGITALIS IN MYOCARDIAL FAILURE WITH SLIGHT DIURESIS (PATIENT 8)

JULY, 1931	WEIGHT, KG.	PULSE, BEATS EACH MINUTE	VOLUME, C.C.	SODIUM CHLORIDE		URINE	
				GM. IN EACH 100 C.C.	GM. IN ENTIRE SPECIMEN	DIGITALIS, GM.	AMMONIUM NITRATE, GM.
8	69.0	88	400	0.08	0.32		
9	68.4	80	650	0.03	0.20		
10	68.0	80	500	0.04	0.20		
11	67.0	82	600	0.05	0.30	0.4	
12	67.0	78	450	0.06	0.27	0.4	
13	68.0	74	425	0.09	0.38	0.4	
14	67.5	70	925	0.22	2.04	0.4	
15	67.3	68	900			0.4	
16	67.3	70	600	0.28	1.68		
17	67.3	69	550	0.67	3.68		
18	68.0	69	1000	0.30	3.00		6
19	67.0	72	500	0.58	2.90		8
20	66.4	82	750	0.44	3.30		8
21	66.4	100	2800	0.75	21.00		8+
22	64.5	100	500	0.17	0.85		8
23	65.2	84	550	0.09	0.50		8

+2 c.c. salyrgan given.

digitalis does cause diuresis, the diuresis resembles that which is obtained by water or urea rather than the chloride diuresis which occurs after ingestion of several diuretics, particularly certain acid-producing salts, caffeine and mercury.

Table VI represents the effect of digitalis in another of the cases of heart failure (patient 8). There was an increased output of urine beginning on the fourth day of administration of digitalis and continuing through the fifth day. Following this, however, the output of urine rapidly diminished. After a rest period of two days, administration of ammonium nitrate was started. The immediate diuretic effect of this acid-producing salt is apparent, and it is to be noted that the diuresis obtained by means of the combined use of ammonium nitrate and salyrgan (mersalyl) far excels the diuresis obtained by the use of digitalis. There was an increase in the concentration of chloride and

TABLE VII

EFFECT OF DIGITALIS AND OTHER DIURETICS IN MYOCARDIAL FAILURE (PATIENT 7)

OCTOBER, 1930	WEIGHT, KG.†	URINE								MEDICATION		
		VOLUME, C.C.	SPECIFIC GRAVITY	SODIUM CHLORIDE, GM.		FIXED BASE, C.C. TENTH NORMAL		TOTAL NITROGEN, GM.		DIGITALIS, GM.	AMMONIUM NITRATE, GM.*	SALYRGAN (MERSALYL), C.C.*
				IN EACH 100 C.C.	IN ENTIRE SPECIMEN	IN EACH 100 C.C.	IN ENTIRE SPECIMEN	IN EACH 100 C.C.	IN ENTIRE SPECIMEN			
11 to 12	91.1	240	1.038	0.11	0.26	42	101	1.58	3.79			
12 to 13	91.4	210	1.033	0.09	0.19	55	115	1.59	3.35			
13 to 14	90.9	850	1.014	0.11	0.93	55	467	0.74	6.29			
14 to 15	90.9	750	1.016	0.10	0.75	52	390	0.77	5.77			
15 to 16	91.2	730	1.015	0.12	0.88	67	490	0.70	5.11			
16 to 17	90.9	670	1.020	0.14	0.94	99	663	0.72	4.82	0.4		
17 to 18	90.4	1050	1.016	0.19	2.00	97	1018	0.57	5.99	0.4		
18 to 19	90.2	950	1.017	0.39	3.70	134	1273	0.52	4.94	0.4		
19 to 20	89.5	700	1.018	0.43	3.01	142	994	0.59	4.13	0.4		
20 to 21	89.2	900	1.017	0.36	3.24	118	1062	0.58	5.22	0.4		
21 to 22	89.1	500	1.018	0.25	1.25	100	500	0.72	3.60			
22 to 23	89.0	550	1.019	0.25	1.38	97	533	0.78	4.30			
23 to 24	88.9	‡									8.0	
24 to 25	89.1	‡									8.0	
25 to 26	88.6	360	1.022	0.14	0.50	122	439	0.69	2.48		8.0	
26 to 27	86.8	2050	1.009	0.61	12.50	138	2829	0.12	2.46		8.0	1.0
27 to 28	86.7	250	1.020	0.11	0.27	116	290	0.77	1.93		8.0	
28 to 29	86.4	380	1.026	0.14	0.53	108	410	1.00	3.80		8.0	
29 to 30	86.1	600	1.020	0.44	2.64	154	924	0.72	4.32		6.0	
30 to 31	83.9	2660	1.011	0.68	18.09	143	3804	0.13	3.46		8.0	2.0
31 to November 1 to 2	83.9	550	1.017	0.23	1.27	112	616	0.30	1.65		8.0	
	83.4	550	1.021	0.10	0.55	115	632	1.00	5.50		8.0	

*Digitalis 0.1 gm. 8 A.M., 12 M., 4 P.M., and 8 P.M.; ammonium nitrate 2 gm. at 8 A.M., 12 M., 4 P.M., 8 P.M.; salyrgan given intravenously.
†Weighed at end of twenty-four hours.
‡Not accurately collected.

in the total excretion of chloride in the urine on the fourth day of administration of digitalis, but this was not nearly so much as that obtained by the use of ammonium nitrate and salyrgan.

The digitalis effect in another of the cases of cardiac failure (patient 7) may be seen in Table VII. This patient had arteriosclerosis, essential hypertension, obesity, and myocardial degeneration with marked cardiac failure. Together with the other usual signs of failure of the circulation, there was marked generalized edema and ascites. After a preliminary period of rest, digitalis was administered in adequate amounts over a period of five days. Definite diuresis was noted the second and third days of administration of digitalis. There was likewise some diuresis on the fifth day of administration of digitalis. Following this, the output of urine diminished and was below that of the control period. After an interval period of five days of rest, the patient was given ammonium nitrate and salyrgan. The superior diuretic properties of the latter drugs in comparison with digitalis are apparent. The average total daily output of urine during the control period was 556 c.c. During the period of five days of administration of digitalis, and the next two days, the average total daily output of urine was 760 c.c., whereas the average for the period of administration of ammonium nitrate and salyrgan was 925 c.c. The patient eventually became completely free of edema by the combined use of ammonium nitrate and salyrgan. The concentration of chloride in each 100 c.c. of urine was increased by the administration of digitalis but did not reach so high a concentration as with the use of ammonium nitrate and salyrgan. The total excretion of sodium chloride in the urine was much greater with the combined use of the latter diuretics than with administration of digitalis. Excretion of fixed base was likewise increased with administration of digitalis, but there was also a more marked increase of excretion of fixed base with the combined use of ammonium nitrate and salyrgan than with digitalis. The excretion of total nitrogen in the urine was changed little, if at all, by use of digitalis, and was definitely diminished during the administration of ammonium nitrate and salyrgan.

A brief summary of the results of digitalis effect in the twelve cases of heart failure is shown in Table VIII.

In studying the diuretic effect of digitalis, patients whose total daily output of urine was 1,000 c.c. or more were classified as showing definite diuresis; those whose output of urine varied from 700 to 780 c.c. were classified as having obtained slight diuresis, and those whose total daily output of urine was less than 700 c.c. were classified as having obtained no diuresis. By this division of the patients, three obtained definite diuresis after administration of digitalis; in four, diuresis was slight, and five failed to obtain any diuretic effect despite adequate therapeutic administration of digitalis. Four patients became com-

TABLE VIII

SUMMARY OF ACTION OF DIGITALIS IN MYOCARDIAL FAILURE

PATIENT	REST PERIOD						DIGITALIS EFFECT						
	EDEMA, GRADE	ELECTRO-CARDIO-GRAM, CARDIAC RATE	PULSE BEATS EACH MINUTE*	AVERAGE DAILY OUTPUT OF URINE, C.C.	AVERAGE AMOUNT OF CHLORIDE IN URINE, GM. IN EACH 100 C.C.	LOSS OF WEIGHT, KG.	EDEMA FREE	ELECTRO-CARDIO-GRAM, CARDIAC RATE	PULSE BEATS EACH MINUTE†	AVERAGE DAILY OUTPUT OF URINE, C.C.	AVERAGE AMOUNT OF CHLORIDE IN URINE, GM. IN EACH 100 C.C.	DI-URESIS	LOSS OF WEIGHT, KG.
1 (first admission)	2	90	80	750	0.74	0	Yes	60	68	1665	0.45	Yes	12.0
1 (second admission)	1	75	76	1395	0.32	2.5	Yes		42	1100	0.20	Yes	1.4
2	3	100	100	800	0.39	0.3	Yes	70	76	1115	0.53	Yes	8.3
3	2	99	80 to 105	510	0.16	0	Yes		84 to 110	1030	0.38	Yes	9.5
4	1	96	82	785	0.48	0.9	No	78	76	795	0.27	‡	2.4
5	3	90	80	790	0.78	2.4	No	71	70	795	0.65	‡	6.1
6	2	60	60 to 70	1365	0.47	3.2	No		60 to 70	765	0.30	‡	4.0
7	3	80	70	555	0.11	0	No	68	100	715	0.28	‡	1.8
8	2	84	80	515	0.05	1.0	No	71	70	635	0.23	No	0.7
9	3	79	80	430	0.70	1.2	No	58	76	550	0.51	No	2.0
10	1		84	845	0.82	7.6	Yes	86	66	585	0.41	No	3.7
11	3	106	90	320		0	No	66	90	635		No	8.9
12	2	95	84	465	0.11	3.5	No		84	545	0.22	No	6.3

*Pulse rate taken 7:30 A.M. on last day of control period and at 7:30 A.M. on the day after the last dose of digitalis.
†Eight months between admission.
‡Slight amount of diuresis.

pletely free of edema following use of this drug, and the edema increased in one case. The average daily intake of extra fluid of the whole group during the time digitalis was given was 774 c.c., whereas the average total daily output of urine was 816 c.c.; the greatest output on any one day was 1,665 c.c., and the least output, 510 c.c. The pulse rate of seven of the twelve patients was slowed following the use of digitalis, varying from four to thirty-four beats to the minute, averaging thirteen beats to the minute. The pulse rate of three patients was not changed, and two patients had an increased pulse rate after administration of digitalis. In the electrocardiogram of each patient was the characteristic sign of digitalis effect described by Cohn. No appreciable change could be noted in the blood pressure in any of the cases following the use of digitalis.

Practically all of the patients showed definite symptomatic improvement following treatment with digitalis. This improvement was evidenced by lessened dyspnea, improved color, the ability to sleep, signs of improvement of the circulation, and general increase in comfort. In general the patients who obtained the best diuretic effect had the most marked clinical improvement. However, some of the patients who had no diuretic effect showed clinical evidence of beneficial digitalis effect. With or without diuresis, patients with cardiac failure may show evidence of marked benefit after the use of digitalis.

COMMENT

The findings in the healthy human subject, under the conditions of these experiments, indicate that digitalis in therapeutic doses exerts slight if any diuretic effect. My data suggest that sodium chloride and water in the diet may be a possible causative factor when diuresis occurs. Definite slowing of the pulse rate following administration of digitalis was observed in all of the five experiments on the three healthy human subjects; the degree of slowing varied from eight to twenty beats to the minute. This is not in agreement with the findings of Cohn. He stated that in the absence of edema reduction in the cardiac rate occurs, principally in the "hypodynamic or unstable heart or the heart which for unknown reasons undergoes spontaneous alterations in rate," and that aside from these the majority of persons do not respond to therapeutic doses of digitalis by a fall in the cardiac rate. Cushny regarded the slowing in cases of normal rhythm as entirely due to the inhibiting action of digitalis.

Despite clinical and electrocardiographic evidence of the effect of digitalis, the diuretic action of this drug was uncertain, even though all the patients had definite myocardial failure and edema. Several of the patients failed to obtain any diuresis after adequate administration of digitalis. In none of the cases was the diuresis so marked as

has been experienced with these and many other patients who have been given other diuretic substances.

In combating the edema of myocardial failure, for some time diuretic substances other than digitalis have been employed in The Mayo Clinic. Since the combined uses of digitalis and other diuretic substances in the treatment of such cases, the results have been much more encouraging.

SUMMARY

Digitalis, when given to the healthy human subject in therapeutic doses and under experimental conditions laid down in this study seems to exert slight, if any, diuretic effect. The diuretic effect of digitalis in cases of cardiac failure with edema is uncertain; such effect may be marked, slight, or absent. It is suggested that in the treatment of congestive heart failure and edema digitalis be employed for its beneficial cardiac effect, and that other substances be also employed for their superior and more certain diuretic action.

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GONOCOCCUS ENDOCARDITIS*

Report of a Case

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SINCE the publication in 1922 of Thayer's[1] comprehensive article on the cardiac complications of gonorrhea, there have appeared in the literature only 12 cases of gonococcus carditis indisputably proved by bacteriological means. In addition to these, six writers have discussed other cases either presenting strong presumptive evidence of this condition or illustrating various methods of treatment after diagnosis. It is the purpose of this paper to report a case in which an unusually detailed history was available and in which a very full post-mortem analysis was carried out; as well as to summarize the recent literature on the subject.

Thayer's series comprised 20 cases either coming under his own observation or collected from the records of Johns Hopkins Hospital, in addition to 60 from the literature. He describes endocarditis of gonococcal origin to be of an ulcerating vegetative nature, usually acute in onset, coming on at varying periods after the initial infection, and pursuing a rapid fulminating course to death in from four to nine weeks, as a rule. The fever is of the high remittent type, a marked anemia develops rapidly, embolic phenomena are usually present, and the constitutional symptoms throughout are very grave.

The age incidence given by Thayer is nine to forty-two years; that in the 13 cases, including our own, reviewed here is nine to thirty-two, the average being twenty-three years. A preponderance of males is noted in the first series; in the later cases the sexes are equally divided. The average duration of the disease is about ten weeks in both instances, though 4 cases are noted by Thayer as exceeding fourteen weeks, the upper limit of the later group. In regard to the anemia, leucocytosis, and embolic phenomena, the statistics originally presented are fully confirmed by subsequent observations. Recent data concerning the precise nature of the renal lesions found seem too indefinite to warrant an attempt at interpretation in this place. Thayer reported the existence of an acute or subacute nephritis in most of his cases, these being more striking the longer the duration of the disease. Arthritis in Thayer's literature was reported in 68.5 per cent of cases; in his own series in only 31.1 per cent; in the 13 cases reviewed here this complication was noted in 6, or 46.2 per cent.

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In only one[2] of these 13 cases was there an absence of definite genital gonorrhea.

In the matter of anatomical distribution of the lesions, it has seemed well to tabulate the various findings:

TABLE I

		JOHNS HOPKINS HOSPITAL (20 CASES)	PREVIOUS LITERATURE (60 CASES)	LATER LITERATURE INCLUDING PRESENT CASE (13 CASES)	TOTALS
Left	A	6	30	5	41
	M	2	15	3	20
	MA	2	8	2	12
	Aorta	2	0	0	2
	Total	12 (60%)	53 (88.3%)	10 (77%)	75 (80.7%)
Right	P	4	1	2	7
	T	1	0	0	1
	PT	0	1	0	1
	Total	5 (25%)	2 (3.3%)	2 (15%)	9 (9.65%)
Both	AP	0	1	0	1
	AT	2	1	0	3
	MT	0	0	1	1
	APM	0	1	0	1
	APT	1	0	0	1
	AMT	0	1	0	1
	AMPT	0	1	0	1
	Total	3 (15%)	5 (8.3%)	1 (8%)	9 (9.65%)
Pericarditis		4 (20%)		3 (23%)	

A = aortic; M = mitral; MA = mitral and aortic; T = tricuspid; P = pulmonary.

Two cases in the Johns Hopkins series showed involvement of the aortic wall as well as of the aortic valve; one similar case is reported in the recent literature.

It has seemed inadvisable to record the occurrence of the acute endocarditis on previously unaffected as against chronically diseased valves, owing to uncertainty in the condensed protocols of some reported cases. Thayer has pointed out, from his observations, a predilection of the gonococcus, in common with the staphylococcus and pneumococcus, for previously uninvolved valves. It should be noted especially that right-sided involvement occurred in only 2[3, 4] of these 13 cases, a percentage considerably less than that observed by Thayer. In view of the anatomical proximity of the pericardium to the endocardium in the neighborhood of the aortic valve, the occurrence of pericarditis in only about one-fifth of all cases seems remarkable.

CASE REPORT

L. L. (Path. 16330), male, aged twenty-three years, was admitted to the urological service of Bellevue Hospital, December 16, 1930, with a chief complaint of swelling behind the scrotum. Five weeks previously he had noticed a urethral discharge,

which had continued without other complication until five days before admission, when a swelling was noted in the perineum. There had been chills and fever for three days, and the swelling had become painful and steadily larger.

Past History.—Patient denied any previous venereal disease. He had chorea at the age of twelve; no tonsillitis or rheumatic fever. In 1928, he noted precordial pain and dyspnea on exertion, with occasional edema of legs, and for a while he ran a temperature up to 102°. In September, 1930, he was admitted to Beekman Street Hospital complaining of stabbing precordial pain, loss of weight, and insomnia. His heart was not enlarged to percussion; the first sound at the apex was sharp and localized; the second pulmonic sound was accentuated, and there was a soft systolic murmur at the apex. Orthodiagram showed slight accentuation of the left auricular curve but no cardiac enlargement. The urine was negative. The hemoglobin was 85 per cent. The leucocyte and differential counts were normal. The Wassermann reaction was negative. There was no temperature. The patient was discharged symptom free after five days' rest in bed.

Family History.—Essentially negative.

Examination.—Local condition: Swelling over bulbous urethra; no fluctuation. Purulent urethral discharge. Prostate slightly enlarged and very soft. General: Pale, somewhat dyspneic, moderately ill-appearing. Heart: Apex impulse felt in the fifth interspace within the nipple line. No murmurs heard. Temperature: 101° F.

Laboratory Findings.—Leucocytes 15,500, 82 per cent polynuclears. Wassermann reaction negative. Blood nonprotein nitrogen 34 mg. Blood pressure 130/70 mm. Phenolphthalein excretion 45 per cent in two hours. Blood culture negative on ordinary agar and meat-infusion broth.

Course.—The perineal abscess was incised, but no pus was obtained. There was no extension of the process; the temperature came down to normal for two days. On the fourth day it rose abruptly to 104.6° F., and the patient was somewhat irrational. Attempts to catheterize were unsuccessful because of stricture of urethra. On the eighth day the patient began to sweat profusely, coughed frequently, and showed several very small petechial hemorrhages in the right conjunctiva, as well as a single one in the left. The heart was seen to be definitely enlarged; there was roughening of the first sound at the apex, and over the aortic area, transmitted to the left of the sternum and toward the apex, was heard a long diastolic, as well and a long systolic, murmur. The pulse was Corrigan in type, and capillary pulsation was noted. The lungs were negative. There was slight edema of both ankles.

A diagnosis of rheumatic heart disease was made and the patient was transferred to a medical ward. The patient looked desperately ill, but a second blood culture was also negative. Marked decompensation set in, and on the fourteenth day the spleen was felt. The temperature was spiking to 105° daily; the urine remained negative. A third blood culture was reported negative. On the twenty-second day the patient was very weak; many petechiae were seen in the conjunctivae, and a fourth blood culture was taken, which was later reported negative. The patient died on the twenty-third day after admission.

Clinical Diagnosis.—Rheumatic heart disease. Acute endocarditis.

Autopsy was performed two hours after death. Anatomical Diagnosis. Heart: Ulcerative vegetative bacterial endocarditis of aortic valve (gonococcus), subendocardial abscess with extension into pericardium, diffuse suppurative and hemorrhagic pericarditis, chronic productive mitral and aortic valvulitis, hypertrophy and dilatation; Kidneys: Acute intracapillary glomerular nephritis, acute focal interstitial nephritis, parenchymatous degeneration; Spleen: Infarction and suppuration (Mx); Brain: Acute suppurative leptomeningitis (Mx); Liver: Parenchyma-

tous degeneration and congestion; Stomach: Suppurative gastritis (Mx); Lungs: Congestion, bilateral hydrothorax; General: Ascites, conjunctival petechiae, gangrene of legs, decubitus ulcer, emaciation, operative perineal scar.

Positive Gross Findings.—Moderate emaciation. A number of small petechial hemorrhages in both conjunctivae; none in other mucous membranes or on trunk or extremities. The lower two-thirds of the right leg and the lower one-third of the left, including the feet, were the seats of a diffuse dusky cyanosis, the line of demarcation about the calves being irregular but definite. There was a superficial bed sore over the left buttock. In the perineum was a recent unhealed operative scar 4 inches in length.

Heart.—The precordium was markedly enlarged. On opening the pericardium about 500 c.c. of opaque brownish fluid material was found free within the sac. There were no pericardial adhesions. The pericardium itself was markedly thickened, injected, and covered with exudate, and the inner surface showed a number of hemorrhages, irregular in outline. The heart showed on its epicardial surface the same changes as noted in the pericardium. Its weight was 420 gm. The right heart was essentially natural. The left auricle was slightly dilated. The contents of the left heart were currant-jelly clot, none of which was adherent. The musculature of the left ventricle was 16 mm. in thickness, of a reddish brown color, without gross evidence of fibrosis. The mitral valve admitted one and a half fingers with ease, and showed a thickened opaque rolled-up edge on which were a row of translucent pinhead verrucae. The chordae tendineae were slightly shortened and thickened, with hypertrophy of the papillary muscles, which showed fibrosis at their tips. There was irregular vascularization of the mitral leaflet.

Attached to and replacing the left anterior cusp of the aortic valve, and extending down on the aortic leaflet of the mitral valve, was an irregular bulky friable vegetation, the total diameter of which was about 3 cm. The vegetation completely destroyed the left anterior valve cusp and ulcerated through the aortic leaflet of the mitral, appearing as an oval-shaped vegetation on the left auricle and the auricular aspect of the mitral valve leaflet. Before the heart was opened, this vegetative mass had filled the lumen of the aortic valve except for an aperture perhaps 5 mm. in diameter. The other two cusps of the aortic valve were thickened along their edges and were fused for a distance of from 1 to 2 mm. at their commissures, but showed no vegetations. The vegetation was adherent to the border of the posterior cusp, obliterating this commissure. Between the left anterior and right anterior cusp, section into the endocardium revealed a pocket between the endocardium and the outer coat of the heart at this point. This pocket contained about 5 c.c. of grayish-red purulent material which appeared the same as that found in the pericardial sac, and it was separated from the inflamed pericardium by a very thin layer of tissue. Except for the above areas, the endocardium of the left ventricle was smooth and transparent. The coronary arteries were narrow and delicate in texture, and were without sclerosis. There were a few raised yellow intimal plaques on the aorta, which for the most part was of normal diameter and elasticity. The iliac arteries were normal as far as their entrance to the thighs; beyond which examination was not permitted.

Lungs.—There were no noteworthy findings except congestion.

Liver.—The liver weighed 1880 gm., was of a red brown color, firm in consistency. Parenchyma was grossly normal except for congestion of the larger vessels. Gall bladder and bile ducts were natural.

Spleen.—The spleen weighed 270 gm., was of a purplish blue color, and on its surface were seen several irregularly circumscribed raised white infarcted areas. On section, these were seen to be wedge-shaped; one involved the entire upper pole of the organ and was broken down and hemorrhagic in its center. Congestion was marked. Lymphoid follicles were very prominent.

Kidneys.—They weighed 380 gm. together, were imbedded in normal fat and connective tissue, were a dull red brown color and somewhat flabby in consistency. On section, the cortex bulged out from a slightly retracted capsule which, however, stripped with ease, exposing a perfectly smooth mottled brown surface without evidence of hemorrhage. The cortex was swollen, and the markings were somewhat obscured. The glomeruli did not stand out prominently. Medulla, pelves, and ureters were natural. No infarcts were noted. The larger renal vessels appeared natural.

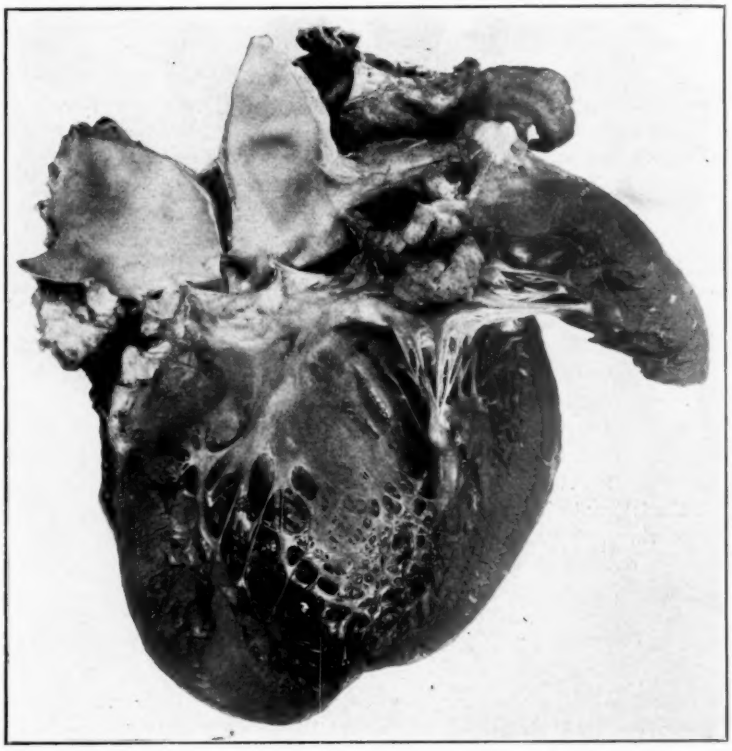

Fig. 1.—Photograph of the heart, opened to show the fungating lesion of the aortic valve.

Bladder, Prostate, and Seminal Vesicles.—No noteworthy changes.

Testes.—Appeared natural.

Adrenals.—Appeared natural.

Gastrointestinal Tract and Pancreas.—No gross abnormalities.

Brain.—Scalp, skull, meninges, and brain substance appeared grossly entirely natural. Section through cortex, internal capsule, and brain stem revealed no recognizable areas of softening or hemorrhage.

Microscopical Examination.—*Heart.*—Sections were cut through all valves, the vegetation, the myocardium of both ventricles, and the auricles. These were first fixed in Kaiserling I, and subsequently mordanted in Zenker's fluid. Paraffin sections were stained with hematoxylin-eosin, by Giemsa's method, by Weigert's method for elastic tissue, by van Gieson's method, by the Gram-Weigert technic, and by Brown's[5] picric acid differential method.

The aortic valve cusp replaced and covered by vegetation in the gross was almost entirely replaced microscopically by a disintegrating necrotic mass consisting mainly

of fibrin and leucocytes, which in Giemsa-stained sections showed enormous numbers of micro-organisms in large colonies as well as discretely. The bacterial colonies were most dense around the periphery of the vegetation corresponding to the aortic valve, and about the upper margins of the sinus of Valsalva. In the center of the vegetation a few strands of necrotic valve substance could be recognized, around which the vegetation was built up. In this necrotic valve remnant no evidence of vascularization could be noted. The necrotic valve remnant was definitely made out in sections prepared with Weigert's elastic stain.

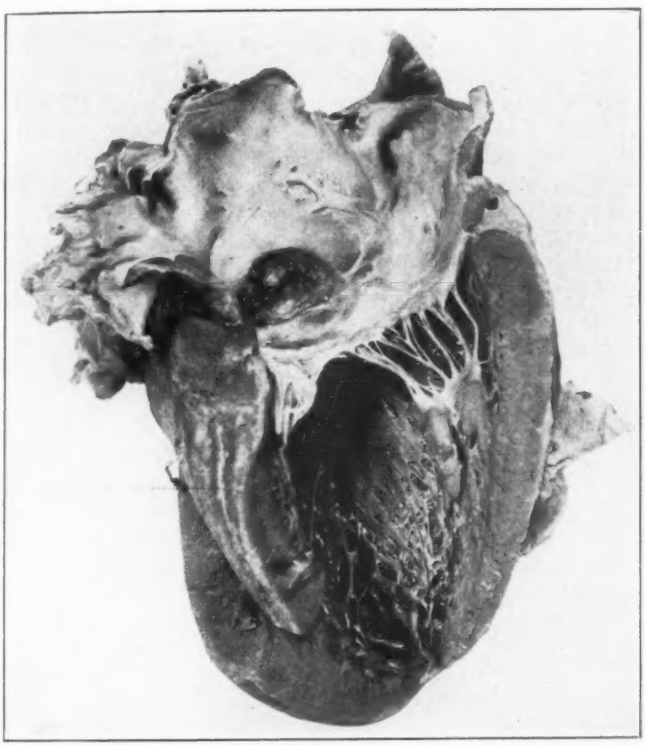

Fig. 2.—Photograph of the heart showing the auricular aspect of the mitral valve leaflet, through which the vegetation has ulcerated.

The aorta above the commissures showed slight roughening of the intima. The media was fairly intact and of normal thickness. The adventitia was markedly thickened by an infiltration of purulent and fibrinous exudate, which was continuous with the mass of necrotic fibrin and bacteria around the commissure. There was a direct extension of the suppurative process in the adventitia to the pericardium covering the aorta. The heart muscle beneath the valve, especially that posterior to it, was fragmented where it merged in an irregular serrated line with the inflammatory tissue. There was in this region considerable invasion of the muscle by leucocytes and bacteria, either isolated or in small groups, and by a growth of granulation tissue rich in fibroblasts and newly formed capillaries. This area showed also a considerable amount of nuclear detritus and degenerating muscle tissue. The base of the aortic valve showed slight fibrous thickening, this fibrous tissue showing invasion by inflammatory cells. Section through the right anterior aortic cusp showed thickening due to the presence of fibrous connective tissue. The base of the valve showed fibrous thickening and, in addition, an infiltration of round

cells, fibroblasts, and a few capillaries surrounded by polynuclear leucocytes. The valve substance was not vascularized.

The inflammatory reaction described above penetrated the septum almost to the point of origin of the tricuspid valve. This, however, was not involved, and presented no noteworthy features. The pulmonary valve showed no abnormalities. Sections through all parts of the heart showed a marked suppurative pericarditis. The pericardium was thickened owing to an overgrowth of granulation tissue rich in capillaries, round cells, plasma cells, polynuclear leucocytes, and fibroblasts which had begun to deposit collagen fibrils. The serous covering was missing, and the granulation tissue was covered by an irregular layer of fibrin. In places, small masses of hyalinized fibrous tissue were seen projecting from the surface. In a few places where the subendocardial fat was scant, the inflammatory process in the pericardium extended into the superficial layers of the myocardium.

The mitral valve showed changes of special interest. The leaflet was definitely thickened. The substance of the valve had an acellular appearance with marked overgrowth of fibrous tissue, and appeared to be entirely covered by endothelium. Strands of elastic tissue could be seen scattered throughout the valve. The cusp was definitely vascularized, the vessels extending from the base into the substance of the valve. The vessels at the valve base were compressed, but showed no intrinsic changes of note except slight thickening. There was no cellular infiltration in this area. The chordae tendineae showed fibrous thickening. In the myocardium of the left ventricle, there were a few small areas where the fibrous tissue of the intermuscular septa appeared definitely increased in amount. This fibrous tissue did not show any cellular infiltration.

The coronary arteries appeared natural throughout.

Bacteriological examination of Giemsa-stained sections revealed diplococci, cocci in short chains and small groups, and short thin bacilli. Sections stained by Brown's differential method showed numerous definite biscuit-shaped gram-negative diplococci, most of which were intracellular. In addition, other organisms were seen as noted above.

Kidneys.—There was a very diffuse and marked tubular degeneration, the lining epithelium being swollen and granular, with desquamation of cellular and nuclear material into the lumina. The glomerular tufts showed a fairly characteristic knotted appearance. The cellularity of the tufts appeared slightly increased. The capillary loops were visible but did not appear to contain any red blood cells, although polynuclear leucocytes were plentiful. There was some swelling of the capillary endothelium. The capsular epithelium for the most part was normal, although in an occasional glomerulus a few cells were swollen and showed proliferation. In most cases the capsular space was well preserved, but in some instances a few polynuclear leucocytes were seen within it. In the interstitium just outside the capsule of almost all the glomeruli there was a thin layer of polynuclear leucocytes. In certain afferent arterioles the endothelium was swollen and the narrowed lumina contained polynuclear leucocytes which were continuous with those in the capillary tufts.

Scattered throughout, and chiefly in conjunction with the pericapsular polynuclear infiltration, there were small focal interstitial collections of polynuclear leucocytes which in places had penetrated to the lumina of adjacent tubules. A careful search through numerous sections of kidney revealed only a single instance where a portion of a tuft appeared to be plugged by an embolus.

The renal arteries appeared natural.

Spleen.—There were multiple infarctions. Thrombi were in many vessels, with exudation of polynuclear leucocytes in considerable numbers into the perivascular parenchyma. The pulp spaces in areas distant from the infarcts showed numerous

polynuclear cells. The lymph follicles stood out very prominently, but were not hyperplastic. No gross bacterial colonies were made out.

Liver.—The liver cells appeared swollen. The Kupffer cells were prominent, their cytoplasms containing small pigment granules. The sinusoids contained polynuclear leucocytes. There was slight passive congestion.

Stomach.—The stroma of the mucosa showed an intense suppurative inflammation.

Prostate and Testes.—Essentially natural.

Brain.—The cortex was natural, although a few vessels showed some perivascular exudation of polynuclear leucocytes. There was marked leptomeningeal congestion, with thickening; numerous polynuclear leucocytes were seen, most of which were around the vessels.

Bacteriological Findings.—As soon as the sternal plate had been removed, the pericardial sac was seared with a knife. About 20 c.c. of straw-colored cloudy fluid were removed with a sterile syringe. Part of this fluid was cultured in hormone broth and hormone agar, while the remainder was used for making smears. The smears made from the unsedimented pericardial fluid revealed numerous pus cells and gram-negative biscuit-shaped diplococci, many of which were included in the pus cells. Both the culture media revealed the same organism in pure culture in forty-eight hours. Postmortem blood cultures were also made in hormone broth medium. Gram-negative biscuit-shaped diplococci were also recovered in forty-eight hours.

On hormone agar plates, the organism grew with the characteristics usually ascribed to the gonococcus. The culture unfortunately died out before sugar tests could be performed.

COMMENT

The situation of the abscess at the commissure, together with the continuity, traced microscopically, of the suppurative vegetation and the inflamed pericardium at the aortic junction, explains the pericarditis; and, in view of the preponderance of aortic lesions in this condition, makes the comparative rarity of the complication noteworthy.[6] Interesting also is the demonstration, in Weigert-elastic-stained sections, of remnants of the aortic valve; no vascularization can be made out, and the vegetative process would seem to be laid down from without, rather than originating as an intrinsic embolism from the primary focus. Although there is no focal myocarditis of the type characterized by Aschoff's bodies, the changes in the mitral valve, with the patchy myocardial fibrosis, and also the old lesions in the aortic valve, point to the existence of a previous inflammatory process, probably rheumatic in type and having as its etiology the childhood chorea. The occurrence of the acute endocarditis on the previously involved aortic valve is relatively rare, according to Thayer.

The kidney changes are those of an early acute intracapillary and extracapsular glomerular nephritis, and of an acute focal interstitial nephritis. These renal changes must be interpreted as being on a toxic or septic rather than on an embolic basis, as the latter phenomenon was observed only in rare instances. The microscopical findings in the meninges; namely, the presence of an early acute suppurative leptomeningitis, were not noted in the gross examination, and prob-

ably represent a terminal process similar to that found in conjunction with pneumococcus endocarditis, where a pneumococcus meningitis is an almost invariable terminal finding.

PROGNOSIS AND TREATMENT

The usually fatal course of gonococcus endocarditis seems well established. Recovery was reported in several cases noted by Thayer, and in a few recent instances. Perry[3] records the case of a young man with a gonococcus bacteremia proved by blood culture, with the physical signs of a pulmonary valvulitis, from which repeated emboli were discharged to the lungs. The patient experienced a very severe reaction following vaccine therapy, which was consequently discontinued; but after the use of repeated small blood transfusions he recovered, the total course of his disease being three and a half months. Jagié and Schiffner[7] report 3 cases of so-called gonococcus myocarditis, characterized by constitutional signs of septicemia, dilatation of the heart demonstrated orthodiagrammatically, and cardiac irregularities. All recovered, but details as to methods of treatment, aside from that of the primary local condition, are lacking. Gonococcus vaccine has been extensively employed, mostly without any beneficial result. Aubertin and Gambillard[8] treated a case unsuccessfully with antigonococcic serum. Kramer and Smith[9] report 2 cases in which sudden death followed six to ten hours after the intravenous injection of mercurochrome; no autopsy was obtained in these cases, and the diagnosis, although strongly presumptive, was unconfirmed by blood culture. One of McCants'[10] patients, treated by intravenous mercurochrome, died suddenly, apparently of a ruptured heart, but autopsy proof was lacking. Electrargol[11] and intravenous metaphen[12] are examples of other therapeutic agents unsuccessfully tried by other authors.

NOTES ON CASES FROM RECENT LITERATURE

The 12 cases submitted in the present summary are indicated by asterisks in the list of references. Riecker's[13] case had its onset seven weeks after the urethritis, an unusually long period. The case of Grenet *et al.*[14] was a nine-year-old girl who had been in the habit of sleeping with a sister who had an active gonorrheal vaginitis; in this case meningitis was also present, due to the gonococcus, the differentiation having been conclusively proved by sugar reactions. The case of Lion and Levy-Bruhl was diagnosed in life by a positive agglutination for gonococcus, this being confirmed after death by cultural methods. Lefebure's[15] case was diagnosed by pure culture from an aspirated purulent pericarditis. A positive complement-fixation reaction was reported in Warfield's[16] case, in which no genital gonorrhea was present at the time of examination. Vigot[17] reports a case of a

man of twenty-nine years dying eight weeks after the onset of urethritis, in which gram-negative diplococci were demonstrated on histological examination of an aortic valve vegetation, all cultures having been negative. McCants[10] found gram-negative diplococci in aspirated pericardial fluid, but cultures were sterile and no autopsy was obtained. Another case reported by the same writer showed a vegetative aortic valvulitis with a purulent pericarditis, but cultures of fluid and blood were negative. The cases of Edwards[18] and of Brebner and Buchanan[19] presented no special features, but carried conclusive bacteriological proof of the diagnosis. One of Pratsikas'[20] cases had a positive blood culture for gonococcus during life; another showed gram-negative diplococci on post-mortem culture of a mitral vegetation, but their identity as gonococci was never definitely established.

SUMMARY

A fatal case of gonococcus endocarditis with detailed autopsy findings is reported. Acute endocarditis followed a urethritis and affected an aortic valve which was already damaged by rheumatism.

In addition to acute vegetative endocarditis of the aortic valve, autopsy revealed chronic productive changes in both mitral and aortic valves, subendocardial abscess with extension to the pericardium, diffuse suppurative and hemorrhagic pericarditis, acute intracapillary glomerular nephritis, acute focal interstitial nephritis, parenchymatous degeneration of the kidneys, infarction and suppuration of the spleen, degeneration and congestion of the liver, suppurative gastritis, pulmonary congestion, bilateral hydrothorax, ascites, conjunctival petechiae, suppurative leptomeningitis, gangrene of the legs, and a decubitus ulcer.

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*Indicates the twelve cases in the recent literature reviewed and summarized in the body of the paper.

THE DIAGNOSTIC VALUE OF EPINEPHRINE IN ANGINA PECTORIS*

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Levine, Ernstene and Jacobson[1] have recently advocated the use of epinephrine to differentiate between angina pectoris and other conditions attended by precordial distress. They found that 1 c.c. of a 1/1000 dilution injected subcutaneously reproduced the attack in cases of angina pectoris but not in their control groups. The T-wave in the angina group increased in height in Lead II, whereas in their control group the T-wave decreased. This last observation confirmed that of Clough[2] who found that while epinephrine occasionally increased the T-wave, it decreased the T-wave in all leads in the majority of cases of normals and patients with "irritable hearts." However, the electrocardiographic changes during spontaneous angina pectoris are not similar to those reported by Levine, Ernstene and Jacobson. Thus, Feil and Siegel[3] have recently pointed out that the characteristic change in the electrocardiogram during an attack of angina pectoris is a depression of the S-T segment such as is seen in coronary occlusion. They found a variable change in the T-wave in their cases, viz., flattening, inversion and increase in amplitude. Cowan and Ritchie[4] reported a flattening and inversion of T-wave during the angina attack. Furthermore, Cottrell and Wood, recently reported that in a case in which they tried epinephrine they obtained so severe a reaction, that they warn against the indiscriminate use of this test.

For these reasons the subject was reinvestigated, on a group of six cases of known angina pectoris, on a group of six normal internes and on a case of "irritable heart" with precordial distress, and one of luetic aortitis with precordial distress.† In every case the patient was put to rest in the decubitus position for one-half hour before starting the observations. Serial electrocardiograms were made; the blood pressure, heart rate and in some cases the respiratory rate were followed and the subjective symptoms of the patient recorded. As a check, in suitable instances, the patient was subjected to a mild exercise to bring on his symptoms.

The results are assembled in tabular form in Tables I, II and III, and characteristic curves are shown in Figs. 1 to 5. In the normal cases, pre-

*From the Heart Station, Michael Reese Hospital, Chicago. Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

†One case of an elderly patient, seventy-eight years of age, is not included because only 0.5 c.c. of epinephrine was used. This dose produced no changes whatever in this patient.

TABLE I

NORMAL CASES

NAME	AGE	RESTING B.P. MM HG.	MAXIMUM B.P. MM HG.	PULSE PRESSURE INCREASE MM HG.	HEART RATE INCREASE PER MIN.	CONTROL EKG	CHANGE IN S-T SEGMENT			CHANGE IN T-WAVE			REMARKS
							LI MM	LII MM	LIII MM	LI MM	LII MM	LIII MM	
Dr. G.	26	118/82	122/55	21	14	QRS slurred all leads, Q_2 and $_3$, T_1 large, T_3 neg., S-T_1 and $_2$ positive	±0	–½	–½	+1 –1	–1	±0	1 c.c. used, palpitation, max. effect 11 min.
Dr. Sto.	31	110/62	124/60	16	4	QRS_3 slurred, T_3 small, S-T_1 and $_2$ positive	±0	±0	±0	–1	–1	–½	1 c.c. used, throbbing in temple, max. effect 12 min.
Dr. Se.	25	114/62	128/48	28	24	QRS slurred all leads, small, Q_3 present, T_3 small and inverted	±0	±0	±0	–1	–½	±0	1 c.c. used, palpitation, discomfort and sticking pain over sternum, max. effect 20 min.
Dr. W.	26	110/70	130/70	20	8	QRS_2 slurred, Q_3, T_3 neg., S-T_3 neg.	±0	±0	±0	–1	–½	±0	1 c.c. used, palpitation, max. effect 18 min.
Dr. Ste.	28	125/85	140/70	30	32	QRS_2 and $_3$ slurred, QRS_3 small, S-T_1 and $_2$ positive	–1	–1	–½	–1½	–1	–½	1 c.c. used, palpitation, precordial distress, abdominal distress, max. effect 25 min.
Dr. E.	23	110/65	120/60	15	16	QRS_3 small and slurred, T_3 small, S-T_1 and $_2$ positive	–1	–½	±0	–1	–1½	–½	1 c.c. used, palpitation, max. effect 24 min.

– Indicates a change in a downward direction.

+ Indicates a change in an upward direction.

TABLE II

ABNORMAL CASES (NOT ANGINAL)

NAME	AGE	RESTING B.P. MM HG.	MAXIMUM B.P. MM HG.	PULSE PRESSURE INCREASE MM HG.	HEART RATE INCREASE PER MIN.	CONTROL EKG	CHANGE IN S-T SEGMENT			CHANGE IN T-WAVE			REMARKS
							LI MM	LII MM	LIII MM	LI MM	LII MM	LIII MM	
R. W.*	67	153/90	158/78	17	12	QRS_2 and $_3$ inverted, slurred all leads, T small all leads, T_3 neg., S-T_1 and $_2$ neg., S-T_3 positive	±0	−½	±0	+½	±0	−½	1 c.c., max. effect 10 min. Pain in middle of sternum and precordum for 15 min.
C. T.†	29	138/84	160/80	18	28	QRS_2 and $_3$ slurred, small Lead III	−½	−1½	−1	−½	−1	−½	1 c.c, max. effect 16 min. Palpitation, ache in thumb, exercise produced more marked effect

*R. W.—Luetic aortitis.
†C. T.—"Irritable heart."
− Indicates a change in a downward direction.
+ Indicates a change in an upward direction.

TABLE III
ANGINA CASES

NAME	AGE	RESTING B.P. MM HG.	MAXIMUM B.P. MM HG.	PULSE PRESSURE INCREASE MM HG.	HEART RATE INCREASE PER MIN.	CONTROL EKG	CHANGE IN S-T SEGMENT			CHANGE IN T-WAVE			REMARKS
							LI MM	LII MM	LIII MM	LI MM	LII MM	LIII MM	
R.P.	48	134/86	138/72	18	12	QRS_2 small, QRS_3 inverted, QRS slurred all leads, T small all leads	±0	±0	±0	–1	+½	+½	1 c.c. used, max. effect 30 min. aur. and vent. extrasystoles produced. No complaints.
J.G.	62	150/90	195/90	45	4	QRS slurred all leads, T_1 small, T_2 and $_3$ neg., S-T neg. all leads	–½	±0	+½	+½	±0	+½ T_3 less inverted	1 c.c. used, max. effect 35 min. Heart conscious.
M.C.	47	130/80	140/80	10	24	QRS slurred all leads, QRS_2 small, QRS_3 inverted, S-T_1 positive	–1½	–1	–½	–2	–1	+1	1 c.c. used, max. effect 30 min. pain in abdomen and chest for 2½ hrs., nitrites not used.
P.J.	42	140/84	146/86	4	16	QRS slurred all leads, Q_3, T_3 neg., S-T_2 and $_3$ neg.	–1	–1	±0	–1	–½	+½ T_3 less inverted	1 c.c. used, max. effect 16 min. No pain, yet a preliminary exercise brought on pain and more marked similar EKG changes.
H.W.	47	155/95	175/105	10	20	QRS slurred and small all leads	–1	–1	–½	–1	–1½	–1	1 c.c. used. max. effect 29 min. Precordial pain, relieved by nitrites.

– Indicates a change in a downward direction.
+ Indicates a change in an upward direction.

TABLE III (CONTINUED)
ANGINA CASES

NAME	AGE	RESTING B.P. MM HG.	MAXIMUM B.P. MM HG.	PULSE PRESSURE INCREASE MM HG.	HEART RATE INCREASE PER MIN.	CONTROL EKG	CHANGE IN S-T SEGMENT			CHANGE IN T-WAVE			REMARKS
							LI MM	LII MM	LIII MM	LI MM	LII MM	LIII MM	
W.P. 1st test	34	135/90	155/90	20	34	QRS slurred all leads, Q_3, T_1 large, T_3 neg., S-T_3 neg.	-½	-1½	-1	-1½	-1	-½ T_3 more inverted	½ c.c. used, max. effect 15 min. Extrasystole felt at wrist after epinephrine, but not recorded. Tightening of chest and pain lasted 41 min. Unrelieved by nitrites.
2nd test		124/78	140/78	16	28	QRS slurred all leads, Q_3, T_2 tiny, T_3 neg., S-T_2 neg.	-½	-½	-½	-½	-½	±0	1 c.c. used, max. effect 15 min. Aur. extrasystole induced pain and tightening in chest radiating to rt. side—lasted 30 min.
3rd test		118/86	174/100	42	32	QRS slurred all leads, Q_3, T_3 neg., S-T_2 and $_3$ neg.	-1	-1½	-½	-1½	-1	+1½ T_3 isoelectric	1 c.c. used, max. effect 15 min. T_3 became isoelectric. Pain in abdomen and slight in chest. Exercise caused similar but more marked changes.

- Indicates a change in a downward direction.
+ Indicates a change in an upward direction.

cordial distress was noted in two of the six subjects following adrenalin. In the angina cases three of the six patients had no pain, although in one of them a typical pain attack was produced by exercise. Of the two abnormal cases (not anginal), one had an attack of pain over the precordium while the other did not. It would seem from these results that the production of pain by epinephrine is not a reliable sign of angina pectoris. Furthermore, the pain when produced in two of three angina cases was long lasting and upset the patients greatly, and in one was not checked by nitroglycerine. Even in the normal cases, one of the subjects had a severe symptomatic reaction presumably because of a susceptibility to epinephrine.

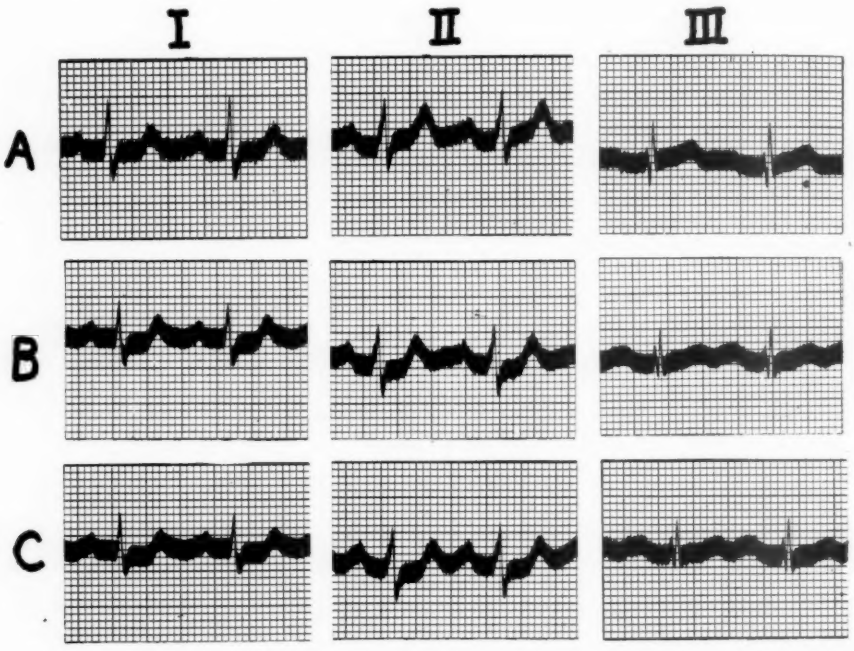

Fig. 1.—Effect of epinephrine on the electrocardiogram of a patient (M.W.) with angina pectoris. *A*, control; *B*, eleven minutes; *C*, nineteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

The most characteristic electrocardiographic change produced by epinephrine in the angina cases was a deviation downward of the S-T interval which gave the electrocardiogram an appearance similar to that seen during spontaneous attacks of angina (Figs. 1 and 2). In one case, however, even this change was absent. However, a similar change was seen in the patient with the "irritable heart" (Fig. 4). In several of the normal subjects, the S-T interval was found to be slightly positive normally and the epinephrine tended to depress it to the isoelectric level or beyond (Fig. 5). It would seem, therefore, that qualitatively there is little difference in the effect on angina patients and others, although

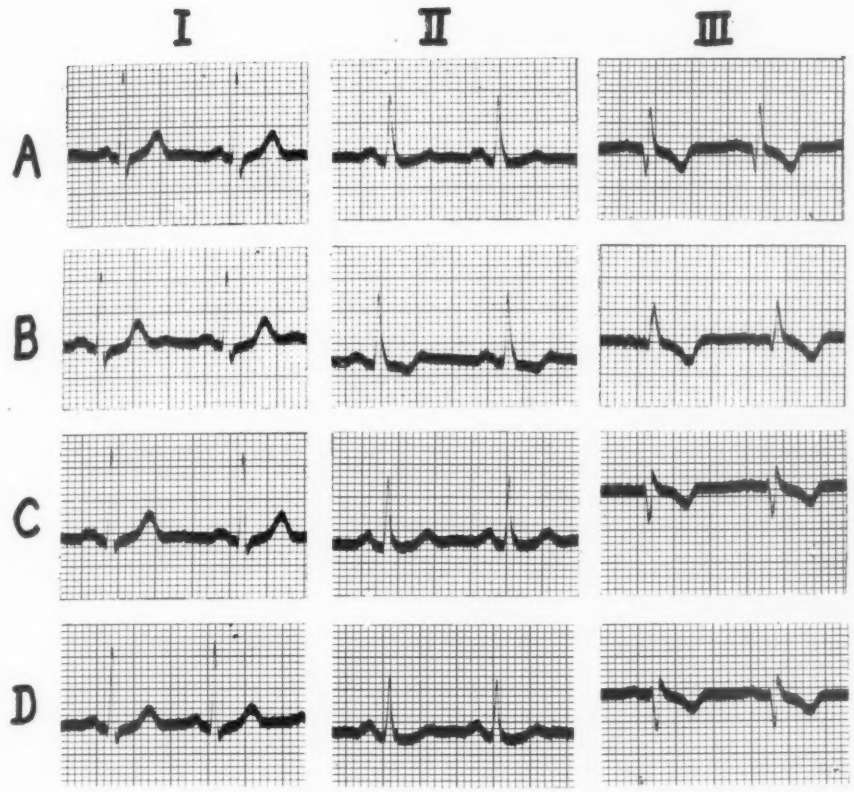

Fig. 2.—Effect of exercise and epinephrine on the electrocardiogram of a patient (P.J.) with angina pectoris. *A*, control; *B*, after standing run which brought on an attack of angina pectoris; *C*, forty minutes later after rest in bed; *D*, sixteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

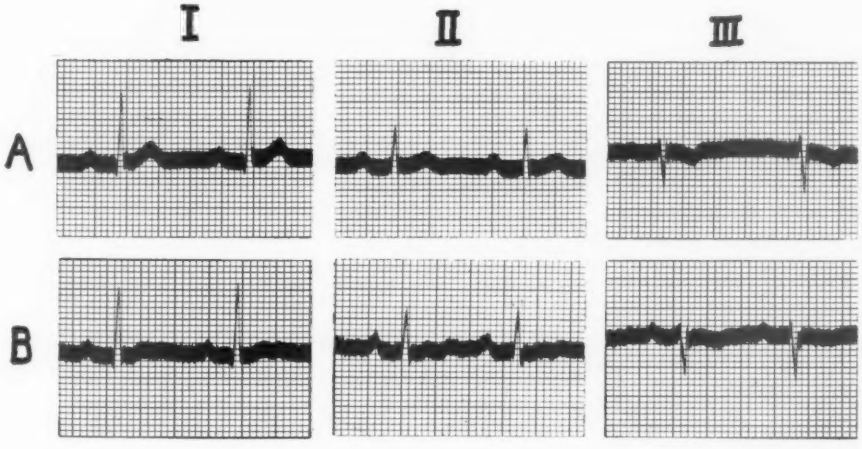

Fig. 3.—Effect of epinephrine on the electrocardiogram of a patient (M.C) with angina pectoris. *A*, control; *B*, twenty-one minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

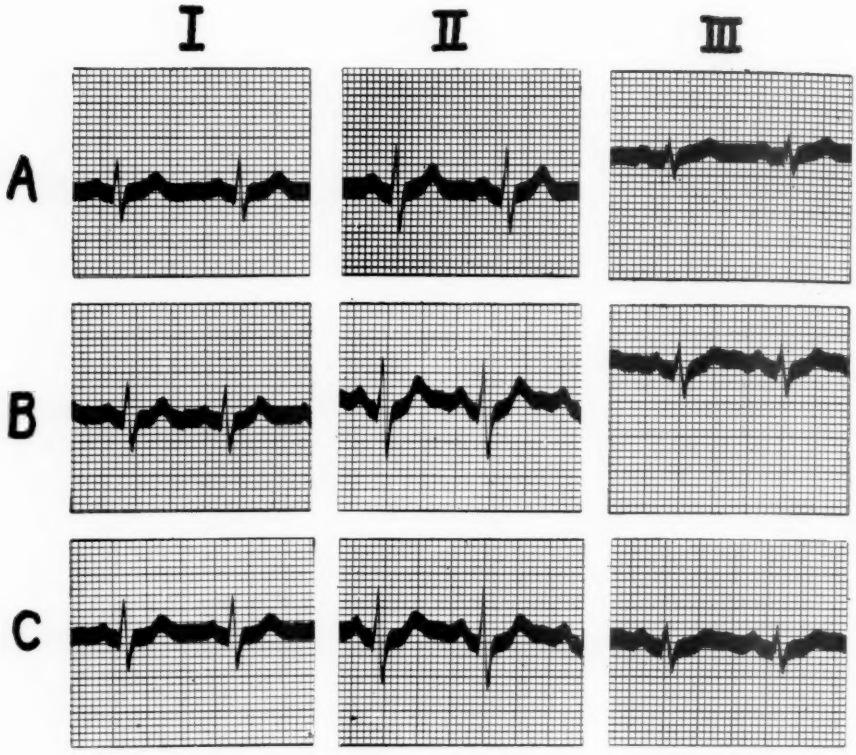

Fig. 4.—Effect of epinephrine on the electrocardiogram of patient (C.T.) with an "irritable heart." *A*, control; *B*, seven minutes, and *C*, fourteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

quantitatively the effect was more marked in the angina patients. The effect of epinephrine on the T-wave was to decrease the amplitude of the wave in practically all the cases, normals as well as angina cases (Figs. 1, 2, 3, 4 and 5) even when the T-wave was inverted to start with (Fig. 3, Lead III). However, in two cases of angina when there was a noticeable left axis shift to start with, the T-wave in Lead III became more upright. In the majority of cases the duration of T decreased.

From these results it seems that the change in the electrocardiogram produced by epinephrine also is unreliable as a test of angina pectoris, although in many cases of angina the change in the S-T segment during epinephrine administration was similar to that occurring during spontaneous attacks of angina pectoris and during those induced by exercise.

The reaction of the blood pressure and heart rate was the same in angina cases and in others except that a drop in diastolic pressure was seen less often in the angina cases (Tables I, II and III).

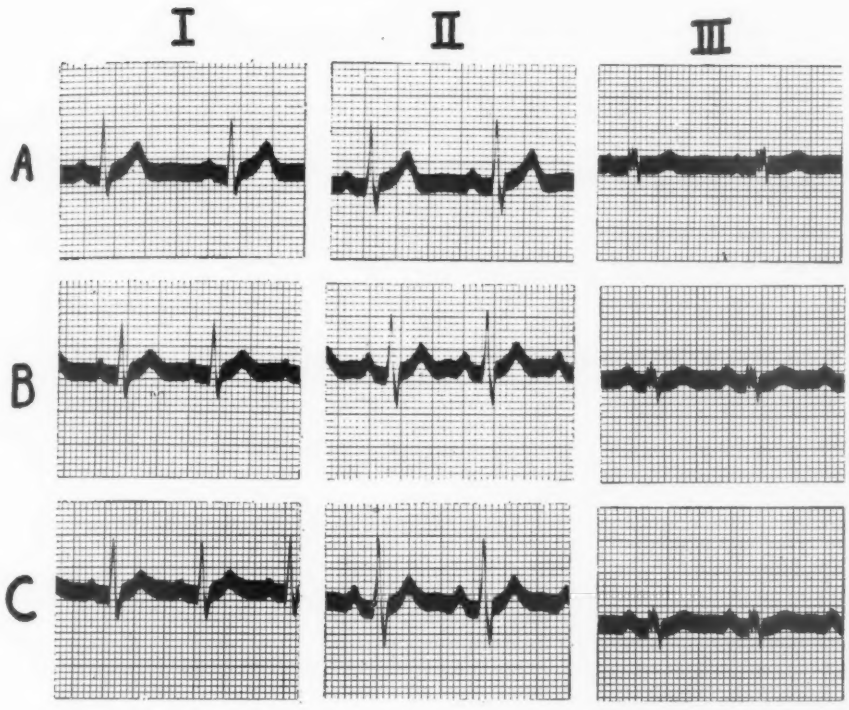

Fig. 5.—Effect of epinephrine on the electrocardiogram of a normal individual (Dr. Ste.) *A*, control; *B*, eight minutes, and *C*, twenty-five minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

SUMMARY

Epinephrine as a test for angina pectoris was found to be unreliable in regard to both the symptoms produced and the electrocardiographic changes. This unreliability makes the test of little value, particularly in view of the severe reactions sometimes encountered.

We are indebted to Dr. S. H. Rubinfeld for assistance and to the six internes who subjected themselves to the test as controls.

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A CHART FOR THE DIFFERENTIAL DIAGNOSIS OF CARDIAC ENLARGEMENT BY MEANS OF THE ROENTGEN RAY*

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IN THE roentgen study of heart disease it is found that distinctive lesions are frequently associated with characteristic changes which can be seen on the film. Tabulation of these changes enhances their

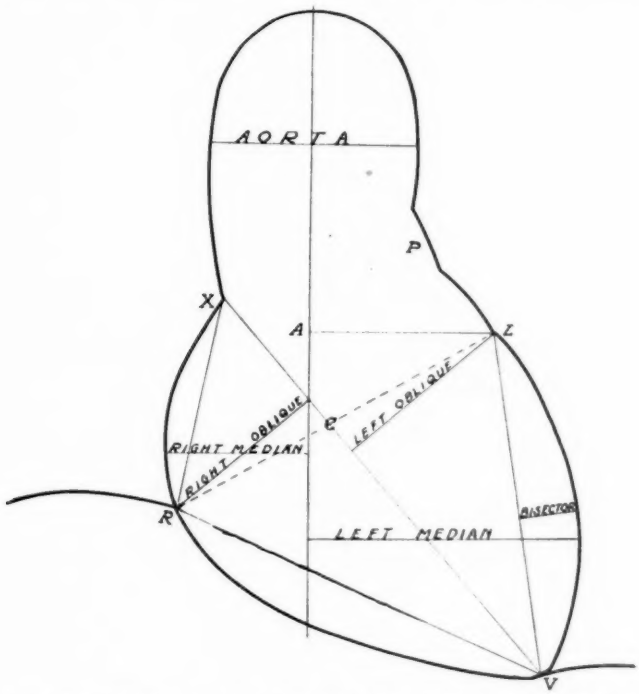

Fig. 1.—*LA*, left auricle; *LV*, left ventricle; *RV*, right ventricle; *RX*, right auricle; *CX* ÷ *CV* = index of auricular ventricular ratio; right median + left median = transverse; *VX*, length; *P*, pulmonary artery.

identification with clinical cardiopathies. The chart is presented to facilitate this tabulation and to indicate a presumptive roentgen diagnosis.

Observations are based both on fluoroscopic studies and on measurements of the teleroentgenogram. The measurements, many of which were derived by Vaquez and Bordet[1] from anatomic landmarks are illustrated in Fig. 1. A line running through the center of the spinous processes serves as a base line. Perpendiculars to this line from the point of greatest distance on the right and on the left, establish the right and left median diameters (or transverse diameter) of the heart.

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*From the Departments of Roentgenology and Cardiology of the Evans Memorial for Clinical Research and Preventive Medicine and the Massachusetts Memorial Hospitals, Boston, Mass.

TABLE I

DIFFERENTIAL ROENTGEN DIAGNOSIS OF CARDIAC ENLARGEMENT

	PULMONARY ARTERY	RIGHT VENTRICLE	TRANSVERSE DIAMETER	LEFT VENTRICLE	BISECTOR	LENGTH	AORTIC PULSATIONS	AORTIC WIDTH	INDEX OF AURICULO-VENTRICULAR RATIO	LEFT AURICLE	RIGHT AURICLE	REMARKS
Normal values		8.5–14.7	9.5–14.5	6.7–8.5	0.6–1.0	11.5–15.0		4.0–6.5	0.534–0.704	4.2–5.0	5.0–6.5	
Pulmonary stenosis	X	X	X									Anatomically shadow may be pulmonary artery or infundibulum. Neither should exceed that of left auricle. Left ventricle not enlarged.
Mitral insufficiency		X	X	X		X				X		Enlargement of heart is transverse.
Tricuspid insufficiency		X	X	X	X							Secondary evidence: hepatic and pulmonary congestion.
Aortitis							X	X				Knob flattened and broadened. Curve of ascending aorta diminished.
Aortic stenosis				X	X	X						Pulsations of aorta are diminished. Contractions of left ventricle increased.
Hypertension				X	X	X	X					Accentuated curve of ascending aorta.
Aortic insufficiency				X	X	X	X	X				Coeur bovinum. Heart shadow centrally placed.
Mitral stenosis									X	X	X	Ventricles not enlarged. Apex pointed.
Myxedema heart		X	X	X	X	X				X	X	Symmetrical enlargement, looks like effusion. Pulsations are of approximately normal amplitude.
Pericardial effusion		X	X	X	X	X				X	X	Symmetrical enlargement, water bottle shape. Pulsations are very faint or absent.

X = Increased.

A line (*VX*) joining the beginning of the right auricular shadow and the apex measures the length of the heart. Perpendiculars to this line from the cardiophrenic angle (*R*) and the auriculo-ventricular junction (*L*) establish the right and left oblique diameters which show the development of the base of the heart.

If *VX* is intersected (at *C*) by a line joining the cardiophrenic angle on the right (*R*) with the auriculo-ventricular junction on the left (*L*), the heart shadow is divided into two areas; auricular area above the line *RL* and ventricular area below it. The length of the segment *CX* divided by the length of the segment *CV* establishes an index of auriculo-ventricular ratio.[2] In normal hearts this varies between 0.534 and 0.704. In the presence of auricular enlargement the index rises to 0.800 or more. When there is preponderant enlargement of the ventricles, the index falls to 0.500 or less.

The lines *RX*, *RV*, *LV*, *LA* show respectively the development of the several chambers, viz., right auricle, right ventricle, left ventricle and left auricle.

The bisector, a perpendicular from the point of greatest bulge of the border of the left ventricle to the line measuring its chamber (*LV*), shows the degree of development of the left ventricular myocardium.

In the application of these measurements to the roentgen diagnosis of heart disease (Table I) it will occasionally be found that not all the positive observations which indicate the lesion in question are present. This does not appear to detract materially from the method of analysis and correlation of roentgen findings herein described. If the salient features of a distinctive cardiopathy are found, and particularly if the clinical evidence agrees, a roentgen diagnosis in terms of the valve or chamber involved may be made with confidence.

If the evidence does not establish a definite diagnosis, it may suggest an error in the roentgen measurements, or the chart may not have been correctly used, or the case is too obscure to warrant a positive diagnosis at the present state of our roentgen knowledge.

The chart may suggest that two or more lesions exist. This may well be, since various combinations are often found in the same patient.

The space limitations of a chart preclude extensive and detailed descriptions. An attempt is made to indicate only the distinguishing characteristics of the various heart lesions. A more detailed account has been presented elsewhere.[3, 4]

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AN INSTRUMENT TO DETERMINE THE DIRECTION OF THE ELECTRICAL AXIS OF THE HUMAN ELECTROCARDIOGRAM*

Based on the Graphic Method of Carter, Richter, and Green

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In 1919, Carter, Richter, and Green[1] described a graphic method for determining the direction and "manifest value" of the electrical axis of the human electrocardiogram. The method makes use of the principle of the equilateral triangle described by Einthoven.[2, 3]

By a slight modification, and its application in the form of a handy instrument (Fig. 1), the method has found considerable usefulness in our hands. The angle and manifest potential of an electrical axis can be estimated in a few seconds. The instrument is particularly valuable for teaching purposes, because it makes possible a ready understanding of the principles of the equilateral triangle and also the visualization of the changes of the electrical axis in a cardiac cycle.

The method makes use of a graphic figure in which an equilateral triangle with the base directed upward is enclosed in a circle, the center of which is also the center of the triangle. Beginning at the midpoint of each side, perpendiculars directed to the three sides of the triangle are drawn through its interior at units representing millimeter intervals. The three sides of the triangle represent the three leads. Lead I, which is the base, is divided into right (positive) and left (negative) sides, corresponding to upward and downward deflections of the electrocardiogram. Lead II, the left side, is similarly divided into halves, an upper (positive) and lower (negative), as is also Lead III. In such a geometric system a line extending from the center when projected on the three sides will give a value on the left side (Lead II) which will equal the algebraic sum of the projections on the other two sides. Since Einthoven[3] has shown that this relationship holds for the human electrocardiogram, that is the values of simultaneous points on the three leads are such that Lead II = Lead I + Lead III; and since the three leads of the electrocardiogram represent the projections of the electrical axes, by substituting simultaneous values on the three sides of the triangle and reversing or projecting toward the interior, the electrical axis is delineated.

The instrument is made of aluminum. Perpendiculars are drawn only to Leads I and III. It is obviously not necessary to draw them to all three leads. The perpendiculars are extended outside the tri-

*From the Department of Medicine, University and Bellevue Hospital Medical College, New York University, and the Third (New York University) Medical Division of Bellevue Hospital.

angle to include values exceeding two millivolts. Attached to the center of the triangle is a revolving arm which is divided into units similar to those which divide the sides of the triangle. This arm extends beyond the surrounding circle. The circle is divided into degrees beginning from a point on the right which forms a horizontal with the center. The values below that zero point are arbitrarily called positive, those above, negative.

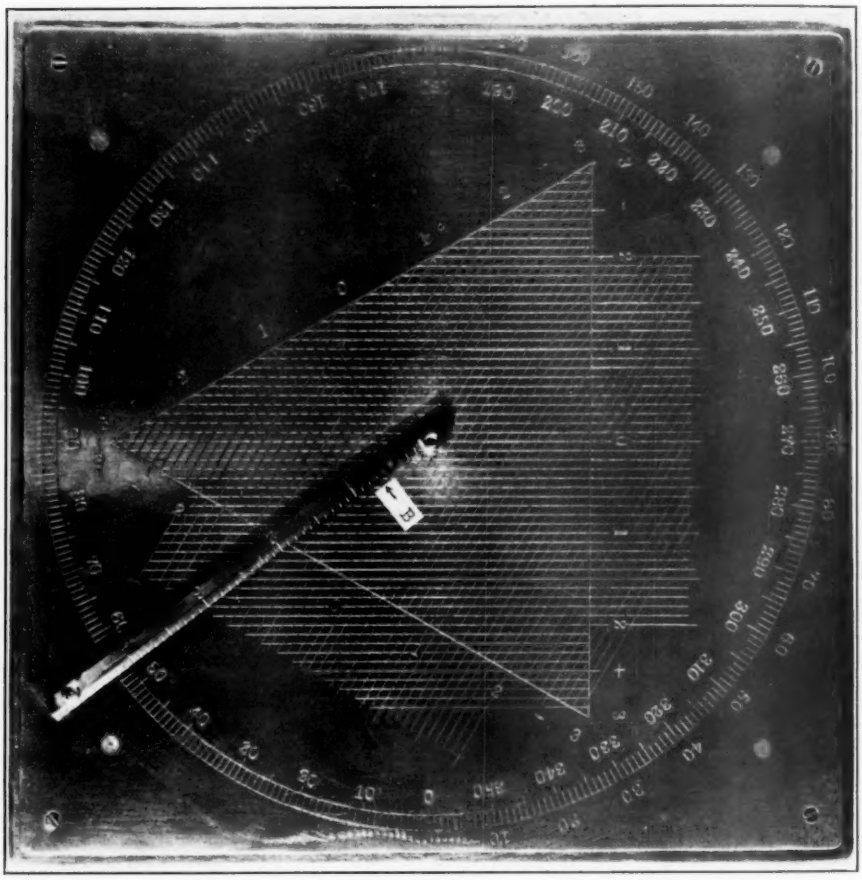

Fig. 1.

Simultaneous values are marked off on Leads I and III. The limits of these values are followed along the perpendiculars. The zero limits will of course intersect at the center, the outer limits will intersect at the outer limit of the electrical axis. By bringing the revolving arm to the point of intersection, the arm will represent the direction of the electrical axis, and on it the value of the manifest potential can be read. The arm will also read off on the circle the degrees the electrical axis makes with the horizontal. Thus, at once both the manifest value and the angle of the electrical axis can be determined.

Example: Points *A* represent simultaneous values on the two leads.

Fig. 2.—The electrocardiograms have been standardized so that every centimeter of deflection represents a millivolt. The value of point *A* in Lead I = 4 millimeters (0.4 millivolts) directed upward;

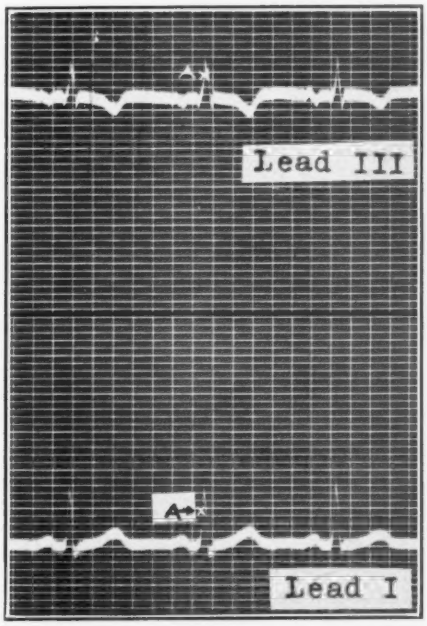

Fig. 2.—Leads I and III taken simultaneously with a Hindle Two Galvanometer Research Model Electrocardiograph. (1/10 second time lines) Lead III top tracing.

therefore measured to the right on the instrument. *A* on Lead III = 3 millimeters (0.3 millivolts) and is also directed upward; therefore measured on the positive side of Lead III. The perpendiculars of these points meet at *B*.

Fig. 1.—By bringing the arm around to the intersection, the manifest value can be read and is equal to 0.7 millivolts. The circle is intersected at +53°; i.e. electrical axis directed downward 53° from the horizontal.

The author wishes to express his appreciation to Dr. A. C. De Graff for his aid in this work.

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Department of Clinical Reports

A CASE OF CORONARY THROMBOSIS WITH TEMPORARY COMPLETE HEART BLOCK*

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IN ORDER to add to the records of disturbances of rhythm in coronary thrombosis the following case is reported.

A male laborer, aged seventy-seven years, with a history of anginal attacks for at least nine years, developed an attack of severe substernal pain after lifting a heavy weight. Pallor, fever, leucocytosis and fall in blood pressure led to a diagnosis of coronary thrombosis. A systolic murmur, not present on examinations prior to this illness, appeared and increased in loudness and roughness over the lower precordium and was associated with a prolonged systolic thrill just within the apex. These findings developed to a maximum by the fifth day and persisted until death which occurred suddenly on the twelfth day. Post-mortem examination was not permitted.

The electrocardiograms are of interest in that they show a complete dissociation between auricle and ventricle on the fifth and the eighth day after the onset of the illness, but a normal auriculo-ventricular conduction time (.20 sec.) on the twelfth day shortly before his death. One can surmise the presence of a thrombus extending into the ventricular cavity in such a way as to cause a systolic murmur and thrill, and an involvement of the auriculo-ventricular bundle by an area of transient tissue pathology which developed on the fifth day to a point of blocking impulses, and had again returned to approximately normal function by the ninth day (clinical return to normal pulse rate), proved by electrocardiograms on the twelfth day.

The case is presented because of two points of interest:

1. A rough murmur and thrill developed over the precordium in the early days following a case of coronary thrombosis.

2. Complete heart block developed on the fifth day and disappeared on the ninth, although the patient died suddenly on the twelfth day.

*From the Department of Medicine, The Nicollet Clinic.

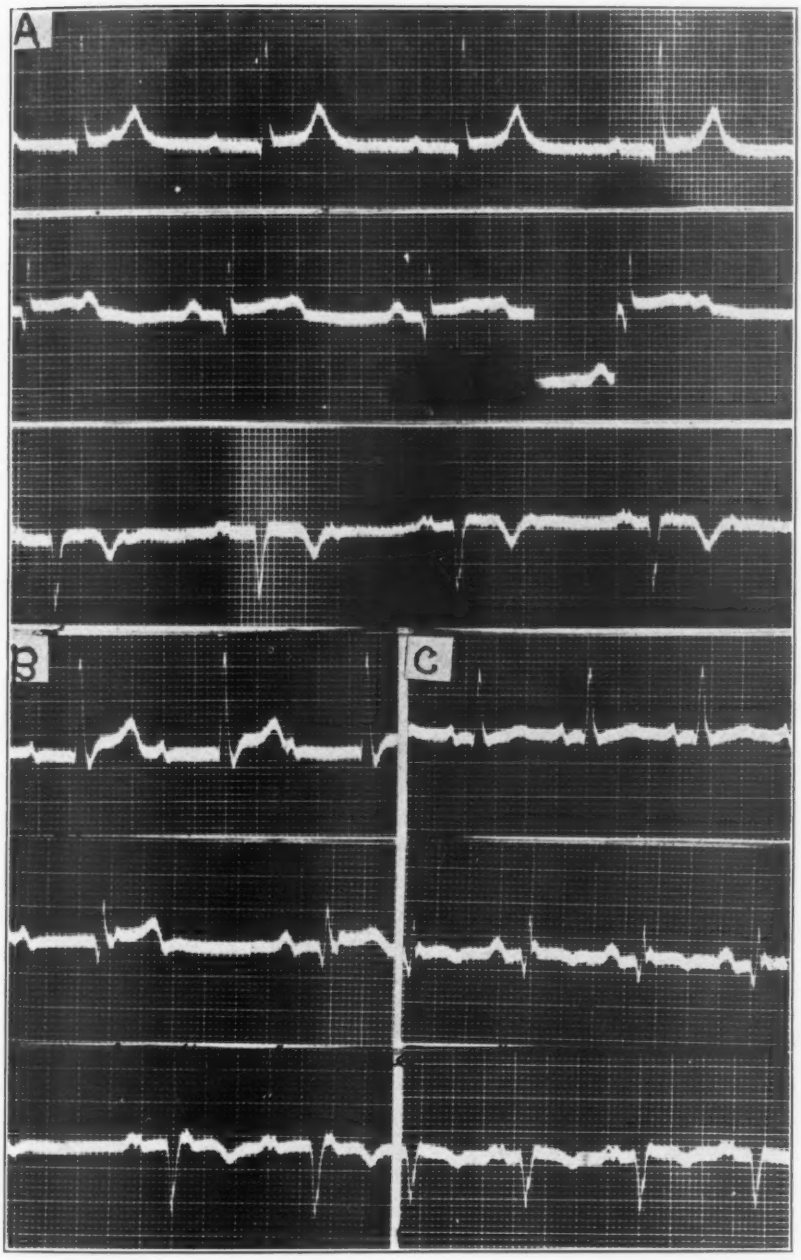

Fig. 1.—*A*. Nov. 19, 1930 (fifth day of illness). Auricular rate 100, ventricular 56, complete dissociation. *B*. Nov. 22, 1930 (eighth day). Partial auriculo-ventricular block with missed beats. *C*. Nov. 26, 1930 (twelfth day). Normal auriculo-ventricular conduction P. R. = .20 sec.

AN UNUSUAL CASE OF LEFT-SIDED DISPLACEMENT OF THE HEART*

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DISPLACEMENT of the heart from its normal position may be congenital or acquired. Of the congenital displacements, the usual form is dextrocardia, which may be due to simple rotation on a vertical axis, or to complete reversion. Rarer forms are incomplete heterotaxy and ectopia cordis. Of the latter there are three forms, according to Ellis[1]—Cervical, with displacement of the heart to the neck; pectoral, with displacement to the anterior chest wall through a vertical slit in the sternum; and abdominal, with displacement into the abdomen through a congenitally maldeveloped diaphragm.

Of the acquired forms, the displacement may be to the right or left and upward. Because the heart is relatively fixed at the base by the great vessels and relatively free at the apex, displacement, to whatever side it may take place, is more or less rotatory and transverse. The greatest movement is at the lower portion, while the basal area may remain in an approximately normal position but rotated.

The extent and nature of acquired displacement will depend, however, more on the causative factor or factors than on the natural resistance offered by the heart attachments. The causative factors in the main are two: pressure and traction. The first includes certain bony deformities of the chest, and some forms of mediastinal and pleuropulmonary disease, such as hydrothorax, pneumothorax, tumors, aneurysms, emphysema, and others. The second includes pleuropericardial adhesions reaching the bony part of the thoracic cavity and extensive enough to overcome the natural resistance to displacement.

The differentiation between congenital and acquired displacement is based upon the character of displacement, associated pathological states, and duration. Acute displacements are easily recognized as acquired. Chronic displacements attributable to adhesions or bony protuberances are likewise easily recognized as acquired by associated chest deformity. When no such pathological conditions are found, the condition may be considered congenital, although in rare cases with a history of thoracic injury in early life, the question of etiology may remain unanswered.

The following case is presented because of its extreme rarity, and of some doubt as to its etiology.

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*From the Department of Medicine, New York Post Graduate Medical School of Columbia University.

CASE REPORT

D. E., male, fifty years old, came to the cardiac clinic of the Harbor Hospital with complaints of occasional pain in the left side of the chest radiating to the left lower scapular region, for the past eight months. The pain had no relation to exertion, was of short duration and mild character. His family history was irrelevant. His personal habits were always regular. He married twenty years ago, had had four children, one of whom died at eight months from some acute disease; the others are well.

A point of interest in his history is that at seven years of age he fell from a third story window and was laid up for several months, the outstanding symptom which he can remember being severe cough. He did not know the real nature of his injuries. Since then, however, he enjoyed perfect health, always working hard, and but once had the "grip" for several days. He was told about thirty years ago that there was something wrong with his heart.

Fig. 1.—Antero-posterior view of the chest. Arrows 1 show the trachea and primary bronchi. Arrow 2 shows the esophagus. Arrow 3 shows the spine. Arrows 4 show the heart and great vessels. The heart, great vessels, trachea, primary bronchi, and esophagus are displaced to the left of the spinal column. The esophagus is seen to approach the center of the spine in its descent. The spine is seen to run somewhat obliquely from above downward and to the left.

The physical examination revealed a well-developed, robust male, of good nutrition and normal color. His pupils reacted normally, and his nose, mouth, throat, and neck were negative. His chest was of normal shape and size, with no bulgings, retractions, deformities, or abnormal pulsations. The lungs were negative, and normal vesicular resonance was heard even over the area which in normal persons is occupied by superficial cardiac dullness. No cardiac dullness was elicited over the normal precordial area, and no visible or palpable apex impulse was present anywhere over the anterior chest. Examination of the left axilla revealed an area of visible and palpable pulsation, about two inches wide in the midaxillary line between the sixth and eighth ribs, and extending from four centimeters from the spine posteriorly to the anterior axillary line. No systolic retraction of the chest wall in this region was visible. The first heart sound was heard best at the area of maximum pulsation, while the second sound was heard best two inches higher. The sounds were of normal intensity and character, and could be heard well throughout the area of dullness. No sounds were heard over the area of the

chest where they are normally expected to be present. No murmurs were heard. His blood pressure was systolic—165, diastolic—100, and his peripheral arteries were moderately sclerotic.

Fluoroscopic examination revealed complete left lateral displacement of the heart, including the basal vessels, trachea, and esophagus, as demonstrated by barium ingestion. All these viscera were lying entirely to the left of the spinal column, except for the esophagus and right bronchus, while in their descent approached the

Fig. 2.—Left posterior-oblique position of the chest. Arrows 1 point to the heart and great vessels. Arrow 2 shows the spine. Arrows 3 show the bronchi and subdivisions. Arrow 4 shows some of the peribronchial infiltration.

Fig. 3.—Left lateral position of the chest. Arrows 1, heart and great vessels. Arrows 2, esophagus. Arrows 3, spine. Esophagus is seen to run inclined anteriorly and to the side of the heart, the cardiac shadow being seen both at the front and behind the esophagus.

center of the spine, and were directed anteriorly. The upper part of the thoracic spine was slightly inclined toward the right. The right dome of the diaphragm was distinct in its outline and freely movable. The left dome was not as distinct in its outline, and merged with the cardiac shadow. Fig. 1 shows the heart and its relations to the trachea, primary bronchi, barium-filled esophagus, and spine. The heart, large vessels, trachea, and bronchi, as well as the esophagus are seen to lie entirely to the left of the spinal column. The right bronchus and esophagus

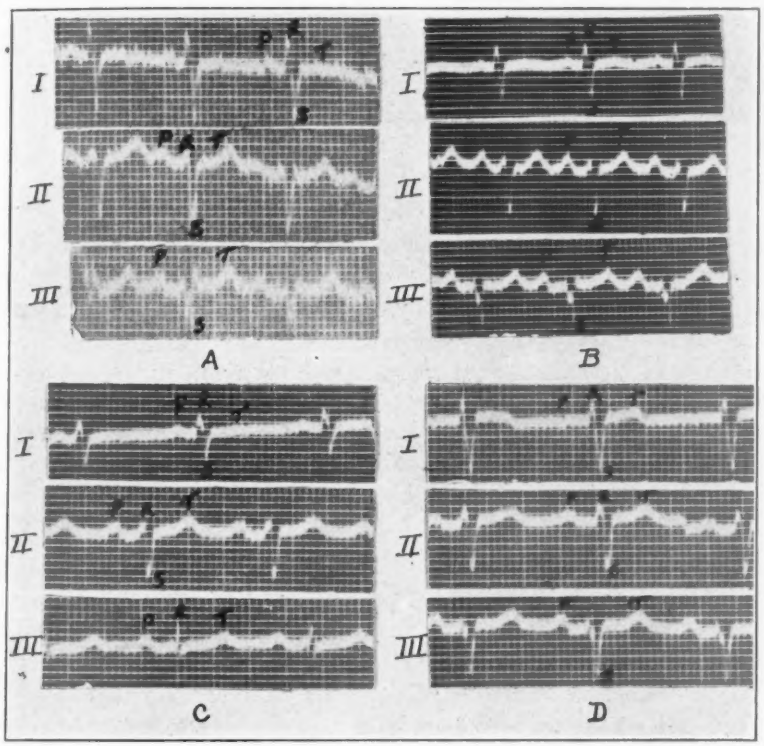

Fig. 4.—Electrocardiograms taken in four postures. *A*, Standing posture; *B*, Dorsal recumbent posture; *C*, right lateral recumbent posture; *D*, left lateral recumbent posture. The major deflection in all postures is downward. No definite direction of the electrical axis is to be made out. There is some change in the heights and direction of the complexes with change in position. The P-R and QRS conduction time are within normal limits.

are seen to approach the midline gradually, in their descent. The esophagus is seen to be compressed at the level of the tracheal bifurcation. Fig. 2 shows the heart and large vessels in the left oblique position. The trachea and bronchi are seen behind the cardiovascular shadow, together with the hilum markings. No such markings are seen to the right of the spine. Fig. 3 shows the organ in the left lateral position. The barium-distended esophagus is seen to be inclined anteriorly and to the side of the cardiac shadow. No visible adhesions are seen in any of the x-ray films.

The electrocardiograms (Fig. 4 *A*, *B*, *C*, and *D*) are unusual inasmuch as no definite direction of the electrical axis can be made out. The auricular complexes appear to be normal, as is the P-R and QRS conduction time. The initial ventricular complexes point predominantly downward in all leads. Changing the

posture of the patient changed the heights of the complexes and to some extent also their direction. The greatest change in direction occurred when the patient was placed in the right lateral position.

COMMENT

A perusal of the literature failed to show a similar case of sinistrocardia, although numerous cases of dextrocardia are on record. Acquired sinistrocardia, due to well-recognized pathological processes does occur, and has been recently described by D'Hour.[2] The underlying cause or causes can, however, be demonstrated in such cases. Besides, in acquired sinistrocardia the heart is placed more transversely, the basal vessels remaining in a more or less normal position, unless they are pushed aside by a big tumor mass in the mediastinum, a condition easily recognizable clinically and on roentgenologic study.

In our case there were absolutely no signs of circulatory impediment or gross pathology of sufficient extent to produce such displacement. Although there is a history of injury in early life with resulting illness for several months, there were no signs of pleuropericardial adhesions to be found on physical, fluoroscopic, and electrocardiographic study, which might be taken as an indication that injury was the cause of this unusual displacement. Although the spine is somewhat obliquely placed, it likewise cannot be considered to be the cause of the displacement, the obliquity being rather opposite in direction to that of the displacement.

From the nature of displacement, involving other mediastinal structures; from its long duration, the patient having been told thirty years ago that "there was something wrong with his heart"; and, from the fact that there was no circulatory or respiratory embarrassment that might be caused by an acquired lesion; also, from the absence of any signs of adhesions, we may conclude that the condition is congenital. As such, there is to my knowledge no other similar case reported. There is one case reported of a congenital defect of the left wall of the pericardial sac[3] with sudden death caused by sudden displacement of the heart through that opening, into the left pleural cavity, during labor. Until this accident the patient was apparently perfectly normal all her life.

The peculiar behavior of the electrocardiogram in the various leads may be accounted for by the fact that the electrical axis does not bear the normal relationship to the standard leads in this case, due to rotation and displacement.

SUMMARY

A case of sinistrocardia, most likely congenital, is reported, which from perusal of the literature appears to be the only one of its kind on record. The outstanding features in the case are: (a) Healthy male,

fifty years old, who had gone through life without any circulatory or respiratory embarrassment; (b) the heart with its basal vessels was entirely displaced to the left of the spinal column; (c) other mediastinal contents, such as the esophagus, trachea, and bronchi were likewise displaced. Although a history of injury is given, it seems to be a mere coincidence, as there is no definite evidence of a pathologic condition present, the nature of which might be considered to be the cause of the displacement.

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SAMOILOFF AND HEITZ

Eminent Contributors to Cardiovascular Literature

Alexander Philip Samoiloff. 1867-1930.

A distinguished worker in the physiology of muscle and nerve and a pioneer in electrocardiography was Professor Alexander Philip Samoiloff of Kasan, U.S.S.R. (Russia), whose death was an unhappy surprise to his many friends the world over. Not only because of his eminence in cardiology but also because of his wide acquaintanceship it is a pleasant duty to publish for his English-speaking friends, and for others too, who may read this Journal, a brief account of his life and accomplishments. Last year in Russia a memorial number of the *Kasan Medical Journal* was published in honor of Professor Samoiloff (April-May, 1931, No. 4-5); the first article was an appreciation by Professor Pavlov of Moscow with whom Samoiloff had at one time worked. This brings to mind a somewhat similar reminiscence in the American Heart Journal in June, 1930, by Professor Samoiloff himself of Einthoven, the inventor of the string galvanometer, whose death occurred in 1927.

Alexander Philip Samoiloff was born in Odessa in 1867. He attended a government high school and then the University of Odessa, from which he was graduated in 1888 as a Bachelor of Natural Science. He entered the Medical School of the University of Derpt the same year, was graduated in 1891, submitted his thesis in 1892, and was thereupon awarded the degree of Doctor of Medicine. For a few months he practiced medicine in Odessa and then spent another few months working in a severe epidemic of cholera in Siberia. From 1893 to 1894 he was assistant to Professor Pavlov at the Institute of Experimental Medicine in Petrograd where he devised some improvements in technic in the operations on animals whose digestive functions were being studied by means of fistulas, and where he made a thorough investigation of Mett's method for the determination of certain ferments. In 1894 to broaden his experience and training Samoiloff transferred to the University of Moscow where he became assistant to Professor Schechinoff who was particularly interested in physical and chemical methods of physiological study. It was here that Samoiloff became interested in physiological physics which led him to spend the rest of his life studying the manifestations, and in particular the electrical manifestations, of the action of muscle and nerve. When Professor Samoiloff was in Boston a few years ago, he gave an address at the Massachusetts General Hospital in the course of which he referred to the importance of physiological studies on heart

muscle, not only for their own value but also because they had proved so often to be pioneer steps in similar studies on other muscle and on nerve tissue.

In 1896 Samoiloff was appointed Associate Professor of Physiology at the University of Moscow and for the next seven years he conducted a part of the course in physiology for the students of the school of medicine and of the school of natural science. In 1903 he was appointed full Professor of Physiology at the University of Kasan in eastern Russia and continued in that position until his death in 1930, although during the last few years he travelled to Moscow frequently to give lectures at the University there to supplement the course in physiology. He always responded to such calls of duty and made especial efforts to keep in touch with his colleagues in physiology in other parts of the world in spite of the great difficulties that surrounded him during and after the Russian revolution. This is attested by his attendance in late years at the International Physiological Congresses in Stockholm in 1926 and in Boston in 1929. It was during his two visits to America in 1926 and 1929 that I derived much pleasure and stimulation from contact with Professor Samoiloff and from acquaintance with his family. Two sons, twin youths, have settled down in America as engineers to carry on the professional activities of the family, while Madame Samoiloff and an older daughter remain in Russia teaching and conducting scientific investigations. A younger daughter is a university student.

Among Professor Samoiloff's contributions to electrocardiography are the following papers:

Elektrokardiogrammstudien, Beitr. z. Physiol. u. Pathol. (Otto Weiss), 1908.

Elektrokardiogramme, Samml. anat. u. physiol., Vorträge u. Aufsätze (Gaupp and Nagel), Jena, 1909.

Praktische Notizen zur Handhabung des Saitengalvanometers und zur photographischen Registration seiner Ausschläge, Arch. f. Anat. u. Physiol. 478, 1910.

Weitere Beiträge zur Elektrophysiologie des Herzens, Arch. f. d. ges. Physiol. 135: 417, 1910.

Vorzüge der mehrfachen Ableitung der Herzströme bei Elektrokardiogrammaufnahmen illustriert an zwei Beispielen, Arch. f. d. ges. Physiol. 153: 196, 1913.

Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralstenose, (With Steshinsky, M.) München. med. Wchnschr. 56: 1942, 1909.

Jean Heitz, 1876-1930.

A little more than a year ago Jean Heitz died in Seville, following a brief acute infectious illness while on a visit to Spain to conduct conferences before the medical faculty in Madrid and in San Sebastian and Barcelona. His death came as a shock to his friends and associates who had expected him to have many more years of active work in study and practice. He had edited the French heart journal—*Archives des maladies du coeur, des vaisseaux, et du sang*—from the date of its creation in 1907 to his death, carrying it on even during the Great War while he was at the front.

Born in Paris in 1876, the grandson of a physician, Heitz was a brilliant scholar even in his early childhood. In 1895 he studied medicine under Hayem, Netter, and Seglas and completed his medical training under Landrieux, Michaux, Dejerine, Merklen, Bezançon, and Babinski. It was in the service of his master, Pierre Merklen, that his interest in cardiology began, and that his idea came to create a physiotherapeutic establishment in France for patients with heart disease.

In 1903 he published his inaugural thesis "Les nerfs du coeur des tabetiques" for which he was awarded a silver medal. That same year he was named laureate of the faculty of medicine and installed himself at Royat after a visit to study the organization of the baths at Nauheim. Royat under the direction of Jean Heitz became the French health resort for patients with hypertension, and there Heitz carried on clinical investigations on hypertension and other aspects of circulatory disease. In 1907, as noted above, he became editor of the newly founded *Archives des maladies du coeur.*

From 1914 to 1919 he took an active part in the French military medical service, carrying on in connection with this service investigations on arterial lesions with Babinski, Labbé, and Letulle. It is for his work on arterial obliteration that he received the Bourceret Prize in 1926. Soon after the war, in July, 1919, he received the cross of the Legion of Honor.

From 1919 until his death in 1930 Heitz spent most of his time at Royat but studied in Paris during the winter months. He served as president of the Medical Society of Royat during the years 1927 and 1928 and in 1929 became president of the Society of Hydrology of France.

Not only in medicine was Heitz an able student and contributor but also in literature and art. Articles from his pen on Stendahl and Balzac were much appreciated in literary circles, and he took great delight in gathering together a fine library.

In writing this brief review of the life of Jean Heitz I wish to testify to the charm of his character, to the warmth of his hospitality during the war and afterwards, and to his great kindness in affording opportunities of seeing some of the heart work in France and of studying rare volumes in his fine library.

Paul D. White

Department of Reviews and Abstracts

Selected Abstracts

Seegal, David, Seegal, Beatrice Carrier, and Jost, Elizabeth L.: Local Anaphylactic Inflammation in the Rabbit Pericardium, Heart and Aorta. J. Exper. Med. **55**: 155, 1932.

An intense inflammatory reaction in the pericardium, heart and intrapericardial aorta can regularly be produced in a sensitized rabbit by the intrapericardial injection of homologous antigen. The appearance of this reaction in sensitized animals is a manifestation of the Arthus phenomenon. The appropriate union of antigen and antibody in such an area as the pericardial cavity leads to striking changes. Gross changes were present in thirteen of the seventeen sensitized animals studied. The lesions of "spontaneous interstitial myocarditis" could be found after careful study in about one-half of these animals.

The authors believe that a possible explanation for the development of the myocarditis in these animals may be found in previous work which showed that such a substance as trypan blue would extend back through the rabbit heart after intrapericardial injection. They believe that the diffusable antigen in the present experiments might pass through the myocardium and produce the changes noted in the heart.

Criep, Leo H.: Electrocardiographic Studies of the Effect of Anaphylaxis on the Cardiac Mechanism. Arch. Int. Med. **48**: 1098, 1931.

Electrocardiographic changes in the guinea pig are analogous in artificial asphyxia and anaphylaxis. The changes consist of bradycardia, partial and complete block, inversion of the T-wave, with a shortened R-T interval and a high T-wave take-off and auricular and ventricular fibrillation. The changes in the T-wave are not unlike those noted in coronary occlusion and suggest the possibility that disturbances in the cardiac mechanism may be due to myocardial anoxemia. The foregoing conclusions are also true of the rabbit during asphyxia, during anaphylaxis and in a condition following clamping of the pulmonary artery.

Microscopic sections of the hearts of guinea pigs and rabbits revealed nothing of note as a physical basis for the changes observed. The vagus nerve does not seem to play an important rôle in the production of the disturbances in mechanism. The functional cardiac changes observed in the guinea pig and rabbit during anaphylaxis are not specifically due to the anaphylactic state but rather to the state of asphyxia that anaphylaxis induces.

Tuohy, E. L., and Eckman, P. F.: Aortic Stenosis With Calcareous Nodules in the Aortic Valves. Minn. Med. **14**: 289, 1931.

Post-mortem findings in three patients are presented. These findings consisted of greatly enlarged hearts with isolated changes in the aortic cusps inducing high grade aortic stenosis. Associated with these changes was constantly found an associated (secondary) aortic insufficiency. Three other cases without postmortem examination

also are included in the report. The same findings on physical examination have been observed, and a probable diagnosis of a similar change in the aortic valve has been made.

The distortion in the aortic cusp was found to be due to nodular calcium deposits. The manner of the deposition of this material is discussed. This lesion and the resulting syndrome may account for typical attacks of angina pectoris in which the coronary vessels have shown no change.

In these patients there has been an absence of rheumatic history, and the other valves in the heart were found to be normal.

The degree of enlargement of the left ventricle to be found in patients with aortic stenosis should lead one to investigate such very large hearts for evidence of calcareous nodular deposits in the aortic cusps. Importance and value of careful attention to heart outlines and in clinical cases to presumptive weights are discussed.

Coombs, Carey F.: The Work of the University Centre of Cardiac Research. Bristol Med-Chir. J. 48: 179, 1931.

The scope of the work together with some of the results obtained in the past four years at the Cardiac Centre are described in this brief report. The following facts have been observed and are worthy of note. During the three years under review, Bristol's population of about 400,000 included 750 children with rheumatic heart disease, while the surrounding country with about 1,100,000 inhabitants had 350 of these children, the incidence in the city being six times as high as in the country. Observations have shown that the infective agent enters the cardiac tissue by way of the coronary blood supply, as shown by the damage occurring in a majority of cases in the arteries and at the root of the aorta. One paper on abdominal manifestations supports the view that the peritoneum is occasionally attacked by a rheumatic infection.

It is believed that ulcerative endocarditis is for the most part a terminal infection. It is believed that in cardioaortic syphilis, apart from gummata which are rarely seen in the heart, the present lesion is an aortitis which injures the heart not only directly by depriving it of the health it is entitled to expect from the aortic elasticity but also by infiltrating the bases of the aortic cusps which are thereby rendered incompetent and by narrowing the mouths of the coronary arteries and thus starving the myocardium. The virus whether spirochete or toxin or both is brought to the aortic wall by the lymphatics which surround it.

Leary, Timothy: Early Lesions of Rheumatic Endocarditis. Arch. Path. 13: 1, 1932.

As county medical examiner, the author was able to study the early phases of rheumatic endocarditis in persons who came to violent deaths while in apparent full health, or who died suddenly without hospitalization and on whose cardiac valves were found the early lesions of rheumatic endocarditis. The principal material was obtained from three patients: the earliest phase from an apparently healthy boy of six years, whose death was due to violence, with an endocardial lesion of the mitral valve before verrucа formation; an intermediate phase from a girl of eighteen years, who had mitral stenosis for eight years before her death, with the endocardial lesion on the tricuspid valve, associated with verrucа formation in various stages; a late phase from a man, aged fifty-one years, who had an old but not advanced mitral process, with the lesion on the mitral valve and showing pseudoverrucae due to thrombus formation.

There was found an unusual tissue reaction, in the form of a cell palisade along the contact edges of the cardiac valves, which appears to be a specific response of

allergic tissue to an infection. The absence of an acute inflammatory reaction in the tissue of the valve and the apparent efficiency of the defense afforded to the underlying tissue in the presence of infecting organisms on the surface are striking.

It is believed that the formation of the cell palisade and the production of verrucae result from injury to the surface of the valve and not from injury arising within the valve. The evolution of the verrucae from local regions of damage of the defensive palisade is described.

Shookhoff, Charles, Litvak, Abraham M., and Matusoff, Irving: Paroxysmal Tachycardia in Children. Am. J. Dis. Child. 43: 93, 1932.

Four cases of paroxysmal tachycardia in children are reported. Three of the cases showed paroxysmal auricular flutter and one paroxysmal tachycardia. The latter case showed evidence of severe rheumatic myocarditis and endocarditis, of which the occurrence of the paroxysmal tachycardia was one of the early symptoms if not the first symptom.

The authors are inclined to believe that the occurrence of these disturbances of mechanism are due to disease of the myocardium and that they have considerable importance in the prognosis of these cases. While such children may live for many years, it would seem that the association with myocarditis would shorten their expected duration of life. The differential diagnosis between paroxysmal auricular flutter and other types of paroxysmal tachycardia is discussed.

Morse, John Lovett: The Prognosis of Acute Endocarditis in Childhood. An Analysis of One Hundred Cases. Am. J. Dis. Child. 42: 735, 1931.

Of 100 children seen during the first attack of acute endocarditis from ten to thirty years before this article was written, 36 are dead, 3 are cardiac invalids, 61 are alive and well. Thirty-seven of those who are alive and well have normal hearts, 18 have slightly damaged hearts, and the hearts of 6 were not examined. The age at the time of the onset of the disease and the intervals elapsing between the onset and the time when the patients were first seen had no apparent influence on the prognosis. In the cases in which rheumatism seemed to be the cause, the results were not so good as in those in which the apparent cause was an infection of the upper respiratory tract. Myocarditis and pericarditis were unfavorable signs. Recurrences of the rheumatic infections were not as common as is usually believed, and repeated attacks did not always prevent recovery. Only one of the patients who are alive and well has a diastolic mitral murmur.

Tallerman, K. H.: Abdominal Manifestations in Rheumatism. Brit. M. J. 2: 844, 1931.

In view of the frequency with which rheumatism occurs in children of the hospital class and the number of times one is confronted with a child suffering from abdominal pain without other signs or symptoms, it is worth while considering how often children with these abdominal symptoms may be actually suffering from rheumatism of which this pain is at the time the only manifestation.

Two cases are reported which give findings suggestive of this situation. It is felt that cases similar to those described probably occur more frequently than is generally recognized.

Weiss, Morris M.: The Electrocardiogram in Children with Chronic Rheumatic Heart Disease and Heart Failure. Am. J. Dis. Child. 42: 1339, 1931.

An analysis was made of the electrocardiograms of eighty-seven afebrile children with chronic rheumatic heart disease and regular sinus rhythm. The average height

and duration of the P-wave were greater than normal in all leads, owing to the predominance of cases of mitral stenosis and insufficiency. Notching of the P-deflection was frequently associated with the cases of mitral stenosis and those showing decreased functional activity. Notching was also associated with tall and long P-waves. The auriculoventricular conduction time was increased in 30 per cent of the cases. No other disturbances in intraventricular conduction were noted.

Spontaneous variations in the T-wave which were found to occur when daily records were taken must be considered when digitalis studies are made in children.

Right axis deviation was found in 60 per cent of the patients with mitral stenosis.

It is felt that routine electrocardiograms had only a confirmatory diagnostic value. An abnormal electrocardiogram had a definite prognostic importance since the largest and longest P-waves and those records that showed notching of the peak in all leads occurred with the greatest frequency in the groups of children suffering with advanced heart failure.

Seham, Max, Shapiro, M. J., and Hilbert, Eunice H.: The Early Diagnosis of Rheumatic Heart Disease in Children. Am. J. Dis. Child. 42: 503, 1931.

In 809 patients admitted to the Lymanhurst Cardiac Clinic during a period of seven years, 46 per cent of the cases were diagnosed as organic heart disease and 54 per cent as no heart disease. Of 379 cases of organic heart disease, 18 per cent were congenital lesions of the heart, 74 per cent were rheumatic in origin, only 3.6 per cent were due to other causes, and 4.4 per cent were undiagnosed. According to the statistics in this study, the most reliable means of diagnosis is the history. A questionnaire used in the study gives more positive data than informal questioning. In 92 per cent of the cases of early mitral disease, it was possible to obtain a history of rheumatism according to the definition used.

The problem of differential diagnosis revolves chiefly around the children who present the following conditions: (1) a systolic murmur with or without circulatory signs and symptoms, (2) rheumatism and a systolic murmur that has escaped carditis, (3) rheumatism and a systolic murmur that ultimately develops into chronic endocarditis, and (4) congenital heart disease, especially patency.

Various methods of examination and functional tests of heart efficiency are discussed. The authors have used esophagrams and have developed a cardiothoracic index. They believe that socalled functional heart tests are of no value in determining the myocardial efficiency of the heart.

Shookhoff, Charles, and Taran, Leo M.: Electrocardiographic Studies in Infectious Diseases. II. Scarlet Fever. Am. J. Dis. Child. 42: 554, 1931.

Fifty hospital patients with scarlet fever admitted consecutively were studied. The observations showed that there is a comparative infrequency of electrocardiographic evidence of myocardial involvement, that there was no tendency for abnormalities when present to persist and that there was no prolongation of the P-R interval.

Sutton, Lucy Porter: The Treatment of Chorea by the Induction of Fever. J. A. M. A. 97: 299, 1931.

Twenty-four cases of chorea have been treated with intravenous injections of typhoid paratyphoid vaccine as a means of producing protein shock fever. There has been prompt cessation of the symptoms, and the course of the disease in these patients has seemed to be greatly shortened. In the cases reported, the average duration after treatment was started was from eight to nine days. A comparison has been made of children treated by this form of therapy with those treated by phenyl ethyl

hydantoin. The protein shock fever appears to have definite advantages over drug therapy. The procedure for the treatment is outlined in this article.

Waggoner, R. W.: Sydenham's Chorea. Am. J. M. Sc. **182:** 467, 1931.

The author has made a study of chorea occurring in a series of 125 patients. The incidence was twice as high in females as in males and was noted to occur chiefly between the ages of five and fifteen years. In addition to the characteristic movements, it was noted that the disease was practically almost always associated with mental symptoms during the acute stage. It is pointed out that these variations of normal personality reactions may have been accentuated rather markedly by ill-advised handling and treatment particularly in the home before the diagnosis was recognized. It was also observed that the disease most likely occurs in individuals in whom there is a predisposition which is the result or the cause of a poor integration of the cerebrocerebellar motor mechanism. Pathologically it is a type of encephalitis characterized by involvement of both the cortex and the basal ganglia but particularly of the corpus striatum and perhaps the corpus Luys.

The most essential part of the treatment of chorea is absolute mental and physical rest, best obtained by the removal of the patient from his home and placing him in an institution where his environment can be properly controlled. The multiplicity of treatments suggested are evidence of their inadequacy. The removal of the foci of infection is important but should be delayed until the child has become accustomed to his new environment, until there has been a diminution in the movements exhibited and until the fever which the patient may have has disappeared.

Weiss, Harry, and Ottenberg, Reuben: Relation Between Bacteria and Temperature in Subacute Bacterial Endocarditis. J. Infect. Dis. **50:** 61, 1932.

The results of a study of the relationship of the temperature to the bacteremia in four cases of subacute bacterial endocarditis indicate that a correlation between these two phenomena probably exists. The phenomena are apparently maintained by a constant, practically uniform feeding of bacteria into the blood stream from the endocardial vegetations and again by the sudden liberation of a large number of organisms into the circulation producing the phemonenon of bacterial showers.

The constancy of the level of the bacteremia is a rather remarkable feature; each case apparently establishing for itself the balance between bacterial invasion and immunologic response which is maintained throughout the course of the disease.

The studies indicate that higher bacterial counts in blood cultures would be obtained if the cultures were made during the periods of low temperature just previous to the expected rise.

Gwyn, Norman B.: Subacute Meningococcal Endocarditis. Arch. Int. Med. **48:** 1110, 1931.

A case is reported that for eight months showed symptoms and physical signs which one is accustomed to associate with infection of the heart valves by *Streptococcus viridans*—subacute bacterial endocarditis. Blood cultures in the last two weeks of the illness were positive for meningococci. Death took place as a result of invasion of the brain and spinal cord by the meningococci.

The observations at autopsy agreed closely with those described as occurring in association with subacute bacterial endocarditis. Meningococci were recovered at autopsy from the meninges only. The lesions in the heart and kidney as described were apprently in accordance with those observations recorded at autopsy in cases of subacute streptococcal endocarditis.

Fulton, Marshall N., and Levine, Samuel A.: Subacute Bacterial Endocarditis, With Special Reference to the Valvular Lesions and Previous History. Am. J. M. Sc. **183**: 60, 1932.

A clinical study has been made of 111 cases of subacute bacterial endocarditis; 30 of these were examined at post-mortem. Only 7 per cent of these cases showed definite clinical evidence of mitral stenosis and 13 per cent of those examined at post-mortem had mitral stenosis. There were 23 instances of mitral insufficiency and 66 of aortic and mitral insufficiency, 10 of which had signs of aortic stenosis as well. There were 5 with congenital abnormalities of the heart, and the remainder consisted of small heterogenous groups. It is important to note that in spite of the great frequency of mitral stenosis as a type of chronic valvular disease, it was found to be associated comparatively rarely with subacute bacterial endocarditis.

The following general rules in regard to the interpretation of murmurs seem apparent from this study; first, if no murmur whatsoever is heard over the heart, one can practically dismiss the diagnosis of bacterial endocarditis; second, if only a systolic murmur is heard, the vegetations will be found limited to the mitral valve and adjacent endocardium (this excludes the rare cases of congenital heart disease); third, if there is in addition to a systolic murmur a basal diastolic murmur, one may predict that there are vegetations on the aortic valve and that there may or may not be a similar lesion on the mitral valve.

A previous history of some definite rheumatic infection was obtained in 51 instances. Forty-two had rheumatic fever, 3 had chorea and 6 had both. From an analysis of the degree and duration of rheumatic infection from which these patients suffered, they were found as a group to have been comparatively free from this type of infection for a considerable period of time preceding the development of subacute bacterial endocarditis. Twenty-eight of the 42 patients who had had rheumatic fever had had only a single attack. In these there was an average interval of 17.5 years before subacute bacterial endocarditis developed. It seems that immunity to rheumatic infection revealed in these patients renders them more susceptible to subacute bacterial endocarditis.

The study of the past history of these patients from the point of view of ability to work and of circulatory efficiency showed that the cardiac condition could be regarded as excellent in 76, good in 17, and fair in 10. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis; though there was satisfactory evidence that in 60 cases heart murmurs had been present for a period of years. It is believed that these patients, had they been examined shortly before the development of subacute bacterial endocarditis, would in most instances have shown a murmur.

The following other findings of interest have been recorded in this study. The males outnumbered the females 3 to 2. The average age of the males (35.7) was nine years greater than that of the females (26.9). The average heart weight in the autopsied cases was 489 gm. Significant arrhythmias were rarely found. Only 1 case showed auricular fibrillation and that was a terminal event. The average blood pressure in 92 patients on whom readings were obtained was 118 systolic and 52 diastolic. There were only 4 patients with a systolic pressure over 150 (all of whom had aortic insufficiency) indicating that hypertension is extremely rare in this form of heart disease. There were cases with very peculiar types of onset in which the evaluation of a systolic murmur was a most important clue to the diagnosis.

The patient who is most liable to develop subacute bacterial endocarditis is one who has had a mitral systolic or an aortic diastolic murmur for some years. If he gives a history of previous rheumatic infection, as happens in about half the cases, it is most likely to be a single attack with unusual freedom from recurrences. He

has been able to carry on essentially normal activities, has shown at no time any important irregularities of the heart or evidence of congestive heart failure and has either a low or a normal blood pressure.

Lambert, Alexander: Cardiac Pain and Sudden Death. Am. J. M. Sc. 182: 769, 1931.

In this comprehensive analysis of the subject, the author presents the many causes of sudden death. It is pointed out that the most frequent cause is not cerebral hemorrhage, but some cardiac lesion. It is also observed that sudden death is not of common occurrence in heart disease when all forms of heart disease are considered. A discussion of the cause of cardiac pain is presented together with a possible explanation. It is pointed out that stretching and overdistention of the first part of the aorta and of the coronary arteries are brought about by normal circulatory reflexes which in diseased tissues cause excessive stretching of the aorta before the depressor reflexes bring relief or by overfilling cause over distention of arteriosclerotic walls of the coronary arteries. As long as the circulatory reflexes do not upset the equilibrium between the myocardium and its blood vessels, there is no pain. When, however, the afferent functions of the nerves are adequately disturbed or the myocardium has degenerated so that it cannot under reflex stimulation contract normally, the normal increased rise of blood pressure and the circulatory reflexes produce excessive dilatation of the diseased blood vessels, and pain results when the heart endeavors to answer the demands for increased work.

Brooks, Harlow: Concerning Certain Phases of Angina Pectoris Based on a Study of 350 Cases. Am. J. M. Sc. 182: 784, 1931.

Observations made on a series of 350 cases of angina pectoris conform to those usually recorded by other writers. A discussion of the etiology and the pathological change in the heart and great vessels is included. Diagnosis and various forms of treatment of this condition are also presented.

Robey, William H.: Cardiology, Old and New. New England J. Med. 205: 992, 1931.

This delightful review of the advances made in the study of diseases of the heart is refreshing to one who chooses at times to pause and consider what advances have been made as the result of the intensive effort directed to the care and prevention of heart disease. The change in conception of various conditions, such as rheumatic fever, tonsils and syphilis, shows how much has been learned during the steady progress of the last few decades. While undoubtedly much remains yet to be accomplished, it is still apparent from such a review that progress is being made. Present conceptions of these various questions are carefully and clearly analyzed in this review.

Schwartz, Sidney P., and Levy, Joseph: Digitalis Studies on Children With Heart Disease. IV. The Effects of Digitalis on the Edema of Children With Rheumatic Fever and Chronic Valvular Heart Disease in the Presence of Sinus Rhythm. Am. J. Dis. Child. 42: 1349, 1931.

Sixty-seven children between the ages of four and fifteen years with congestive heart failure and rheumatic heart disease were given variable dosages of digitalis of a potency of 1 cat unit per cubic centimeter to the point of nausea and vomiting and for longer periods when these minor toxic signs did not appear.

All of these children were in the afebrile stage of the disease when these observations were made, and they all had a regular sinus rhythm with a ventricular rate that averaged from a minimum of 66 to a maximum of 110 beats per minute. In approximately one-third of the cases, the experiments were repeated on several occasions at a time when the children had shown increasing signs of congestive heart failure, such as swelling of the face and the abdomen, hydrothorax, ascites and edema of the legs with enlargement of the liver.

A loss of body weight within one week following the use of the drug, with striking improvement in the signs and symptoms, was observed in only one child among the sixty-seven. Even in this case it was not certain that the improvement resulted from the use of the drug. No therapeutic response to digitalis was noted in the other cases.

It is probable that the type and pattern of congestive heart failure following rheumatic fever and chronic rheumatic valvular heart disease are responsible for the refractoriness of these children to digitalis in effective doses.

Wolferth, Charles C., and Wood, Francis Clark: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads. Am. J. M. Sc. 183: 30, 1932.

Many cases of coronary occlusion do not show characteristic changes in routine electrocardiograms. It seems that there are "silent areas" in the heart where infarction may occur without producing a deviation of the S-T interval from the isoelectric line in any of the three conventional leads. The authors found that typical electrocardiographic evidence of cardiac infarction in experimental animals could be recorded by applying the electrodes to the anterior and posterior surfaces of the chest wall. After occlusion of arteries supplying hitherto silent areas, it was possible to determine striking deviations in the S-T interval. These results make it apparent that the anteroposterior chest lead (Lead IV) is an important adjunct to the routine electrocardiogram in the diagnosis of certain cases of coronary occlusion.

Two cases are reported to illustrate the use of this Lead IV. In the first, eight days after the original infarction, there was striking and unmistakable deviation of the S-T interval in Lead IV. In Case II, both Leads I and IV showed evidence of coronary occlusion, Lead IV showing a much more striking S-T interval deviation than that seen in Lead III.

Schultz, Mark P.: The Use of Amidopyrine in Rheumatic Fever. Arch. Int. Med. 48: 1138, 1931.

In the treatment of patients with rheumatic fever in the Hospital of the Rockefeller Institute, it has been found that amidopyrine is decidedly superior to other drugs heretofore employed; namely, sodium salicylate, acetylsalicylic acid, the ethyl ester of phenylcinchoninic acid, cinchophen and neocinchophen. Brief review of the literature concerning it is presented as a preliminary to the account of the observations presented in this paper on rheumatic fever.

Experience indicates that amidopyrine may be employed in daily doses of at least three grams without provoking symptoms of toxicity. Instances of idiosyncrasy are less frequent than with any other drug of this type. In rheumatic fever it has been found effective in patients not relieved by other drugs or unable to tolerate them in the therapeutic doses; and total daily doses of less than two grams have been found adequate in this disease. The feasibility of giving effective quantities without provoking untoward side actions, as well as the wide margin between therapeutic and toxic doses, renders this drug particularly valuable in the treatment of patients with rheumatic fever.

McEachern, Donald, and Baker, Benjamin M.: Auricular Fibrillation. Its Etiology, Age Incidence and Production by Digitalis Therapy. Am. J. M. Sc. **183**: 35, 1932.

A study has been made of the records of 575 patients seen during the past twelve years in whom the electrocardiograms have at one time or another shown auricular fibrillation.

The etiological relationships to the various forms of cardiac disease are tabulated. The infrequent occurrence of the arrhythmia in the first decade of life is described and two additional instances are recorded. Emphasis is laid upon the rarity of auricular fibrillation in syphilitic cardiovascular disease.

In the present series, 35 per cent of the cases were associated with rheumatic heart disease and only 3 per cent with syphilitic cardiovascular disease. Note is made of the production of auricular fibrillation by administration of digitalis.

Stroud, William D., LaPlace, Louis B., and Reisinger, John A.: The Etiology, Prognosis and Treatment of Auricular Fibrillation. Am. J. M. Sc. **183**: 48, 1932.

The present series consists of 253 cases of chronic fibrillators, those having paroxysmal fibrillation or in whom normal sinus rhythm returned spontaneously having been eliminated. The cases have been followed over a period of at least one to eighteen years after the onset of fibrillation. Diagnosis has been confirmed by electrocardiograms in each case.

Throughout the series no common etiologic factors have become apparent. The presence of auricular fibrillation does not necessarily imply a worse prognosis than in the nonfibrillating heart with an equal amount of cardiovascular damage.

The average age of onset of auricular fibrillation due to rheumatic cardiovascular damage was thirty-nine years. The prognosis is very poor in such patients developing fibrillation before the age of twenty-five. Of 65 patients with manifestations of rheumatic cardiovascular disease before the age of twenty-five, 86 per cent had developed auricular fibrillation before the age of forty and 88 per cent had died before the age of fifty-three years. The average age of onset of auricular fibrillation in the arteriosclerotic (nonrheumatic) group is about fifty-nine years. Of the eighty-eight cases, none had begun to fibrillate before the age of forty years, and 72 per cent developed auricular fibrillation after the age of fifty-three years. Fibrillation associated with thyrotoxicosis will usually terminate spontaneously following partial thyroidectomy and, if not, almost invariably will respond promptly to quinidin therapy after such an operation. Syphilitic cardiovascular disease is comparatively rarely associated with auricular fibrillation.

In the treatment of patients with auricular fibrillation, digitalis usually proves most satisfactory. It is only in the exceptional case that a restoration to normal sinus rhythm by quinidin sulphate is of more apparent value to the patient than the establishment of a daily maintenance dose of digitalis. Although there appears to be little danger of accident from the use of quinidin sulphate in properly selected cases of auricular fibrillation, yet the authors feel this drug should be used in those few cases of younger individuals with slight or no demonstrable cardiovascular abnormality except the arrhythmia or in thyrotoxic patients following partial thyroidectomy without a spontaneous return to normal sinus rhythm.

Campbell, S. B. Boyd, and Turkington, S. I.: Right Bundle-Branch Block. An Analysis of the Clinical Records of Fifty-Six Cases With Typical Electrocardiograms. Quart. J. Med. **24**: 481, 1931.

The investigation of this series of fifty-six cases was undertaken with the object of reviewing the signs and symptoms associated with the condition and of obtaining

figures which might prove useful for prognosis. Thirty patients were in the hospital, and twenty-six had been seen in consultation practice. The incidence was roughly 1 per cent of the total patients seen in the same time. No characteristic etiological factor was found in the group. Thirty-six of the cases were men. The average age incidence was about sixty years. The symptoms and signs were those commonly found due to myocardial degeneration. In the hospital group, there was a case mortality of 73 per cent of the cases which could be traced. The second or nonhospital group showed a case mortality of 42 per cent.

Parkinson, John, and Cookson, Harold: The Size and Shape of the Heart in Goitre. Quart. J. Med. 24: 499, 1931.

A consecutive series of 130 patients with goiter causing symptoms was examined with the primary object of deciding the size and shape of the heart by radiography. In addition a series of post-mortem records of 43 goiter cases was investigated to determine the incidence and distribution of cardiac hypertrophy.

Of the forty-three cases of goiter all but three had shown the classical symptoms of thyroid intoxication. There proved to be hypertrophy of the heart in more than one-half. The increase involved both ventricles as a rule, sometimes the left more than the right, occasionally the left alone. A predominant or isolated hypertrophy of the right side was never seen. In general it was the younger patients and those with the shorter duration of symptoms who showed no hypertrophy. It was also in the younger patients, say under thirty years, that the rhythm had been normal throughout or fibrillation had come only as a terminal event.

Established fibrillation occurred in older people with an average age of twenty-one years in eight cases at death. The heart weight was greater on the average in those with established fibrillation than in those with normal rhythm. The greatest increase in heart weight was registered in those with fibrillation and heart failure. When emaciation was extreme, the heart was only slightly or not at all hypertrophied. In the three cases of goiter where the gland had not been suspected of producing symptoms, there was cardiac hypertrophy in two, and perhaps in the third.

Clinical and x-ray observations were made on 130 patients with goiter and symptoms from it. Without x-ray examination it is difficult to determine the size of the heart, especially when there is tachycardia, and either a teleradiogram or an orthodiagram or both were taken of every patient. The criteria of enlargement applied to these records are discussed. Enlargement was found in about 45 per cent of cases, usually slight or quite moderate, but not rarely great. In most it involved both contours of the heart, but more particularly the left and sometimes the left only. Although several cases with striking displacement and some stenosis of the trachea were included, enlargement of the right side of the heart alone was never seen. Electrocardiograms, so far as they can be used as an indication of hypertrophy and its relative distribution, confirmed the radiographic and post-mortem findings.

The incidence of auricular fibrillation, including both paroxysmal and established forms, was 27 per cent. Heart failure was present at some time in twelve, and all these had fibrillation, except one with a complicating hypertension.

A few serial records showing progressive increase in the heart size were obtained, all from patients with permanent fibrillation. Comparison between records taken before and after thyroidectomy was made in eleven cases and gave variable results: there might be no change, an increase, or a decrease in the transverse diameter of the heart. After operation several factors come into play which render it difficult to accept the changes as evidence of actual alteration in heart size.

The form of the heart is often affected in a characteristic way in goiter. Undue prominence of the pulmonary arc was a striking feature of about one-third of the

series, sometimes appearing as a convexity on the left profile, sometimes combining with an enlargement of the heart to the left to render this profile straight. An exaggeration of this arc is often an early change, preceding any enlargement of the heart chambers. Post-mortem measurements showed that the pulmonary artery was often dilated.

The left auricle was not enlarged out of proportion to that of other chambers of the heart—a sharp distinction from the heart of mitral stenosis. The superior vena cava was sometimes prominent; this would be expected with the venous congestion of heart failure, but such an explanation only applied to a small proportion. The aortic arch reached too high a level in the chest in about one-third. The form of the vascular pedicle was modified occasionally by a retrosternal goiter.

When symptoms are mild or of short duration, the heart in goiter is normal in size and shape. When symptoms are severe and of long standing, it is in a fair proportion both enlarged and modified in shape. The greatest enlargement is seen with auricular fibrillation and failure. The special form characteristic of the goiter heart is based upon a combination of prominence of the pulmonary arc, of the left ventricle, and to a minor extent of the right auricle. As a result of these changes, the heart may be generally enlarged, the contour retaining much the same shape as in the normal heart; whereas almost all other forms of cardiac disease causing enlargement greatly modify the shape. In their fully developed form changes in the left arcs produce a distinctive picture with its straight left border and a right auricular arc only slightly enlarged. The heart so disposed, when seen from in front, has some resemblance to a ham. This picture differs from that of mitral stenosis in the relatively slight prominence of the right auricle and the fuller aortic knuckle as seen from the front and in the absence of left auricular enlargement as seen in the first oblique position. It approximates more the cardiac outline of combined mitral stenosis and aortic incompetence.

Radiological examination is a help in judging the presence or severity of a cardiac lesion in a patient with goiter.

The demonstration of cardiac enlargement is important from the standpoint of the surgical treatment of goiter. When present, it is an added reason for, rather than a contraindication to, surgical treatment. Though the greater the enlargement, the poorer is the prospect of a complete return to normal, yet the aid of surgery will often be required to check the progress of the lesion.

In deciding the cause of obscure cardiac symptoms or enlargement, or of auricular fibrillation with or without failure, the discovery of the characteristic radiographic picture may suggest a goitrous etiology.

Harrison, T. R., Calhoun, J. Alfred, and Turley, F. C.: Congestive Heart Failure. XI. The Effect of Digitalis on the Dyspnea and on the Ventilation of Ambulatory Patients With Regular Cardiac Rhythm. Arch. Int. Med. 48: 1203, 1931.

The effect of digitalis has been studied in forty-three patients with regular cardiac rhythm. Most of the patients had never had congestive failure. None of them had more than slight edema at the time they were studied and the majority had none. The following results were obtained: Nineteen patients had paroxysmal nocturnal dyspnea. Sixteen of these persons were completely relieved and one was worse after the drug. Forty-three patients had dyspnea brought on by exertion. Definite benefit was obtained in fifteen of these, apparent benefit in fourteen and no improvement in twelve, and two patients were worse after the drug. In eight subjects the vital capacity, ventilation per square meter on standardized exercise, and ventilation index were studied. Seven of the eight patients reported clinical improvement of some degree, and in all of them measurements of ventilation also indicated improvement.

One patient felt worse after digitalis, and objective study of the ventilation showed that he was worse.

As a result of this study, it is concluded that digitalis is of great benefit in patients with paroxysmal dyspnea and is of some value in many patients with dyspnea brought on by exertion.

The number of patients with rheumatic heart disease was too small to justify generalization in regard to this observation, but patients with hypertensive, arteriosclerotic and syphilitic heart disease were usually benefited.

The observations concerning the ventilation index seemed to indicate that this method of study may be of some general use in evaluating therapeutic measures in patients with cardiac disease. It has been possible to determine whether a given drug was of value in combating cardiac edema because the urine volume could be measured and the patient could be weighed. However, methods of expressing dyspnea quantitatively have not heretofore been available.

Harrison, T. R., Ashman, R., and Larson, R. M.: Congestive Heart Failure. XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart. Arch. Int. Med. **49**: 151, 1932.

A study of ventricular fiber thickness, heart rate and the length of diastole has been made in a number of animals of different species, in normal human subjects of various ages and in human adults with enlarged hearts. It has been found that in all normal subjects a thick ventricular fiber is associated with a slow heart rate and a thin heart fiber with a fast heart rate. It is believed that the slow heart rate in animals with thick cardiac fibers is advantageous because the recovery period of the heart is prolonged. This prolonged period, for example, affords opportunity for the oxygen to diffuse through the thicker fiber.

It was found that subjects with enlarged hearts have heart rates much faster than would seem to be optimal for such thick fibers. These observations suggest that "cardiac fatigue" may be due in part to a heart rate which is faster than optimal. It is believed that this conception may explain why congestive heart failure may occur in the absence of any demonstrable myocardial abnormality other than hypertrophy and dilatation. It is suggested that a heart rate much slower than normal would be of great benefit to patients with hypertrophied hearts.

Macpherson, Walter E., Essex, Hiram E., and Mann, Frank C.: The Rate of Disappearance of Glycogen During Contraction of the Perfused Heart of the Rabbit. Am. J. Physiol. **99**: 429, 1932.

Rabbits' hearts were analyzed for glycogen content. The hearts were cut into sections, and the glycogen was ascertained for various levels. A series was analyzed for control purposes, another series was perfused with Ringer-Locke solution, containing glucose, and a third series was perfused with the same type of solution but free of glucose. The methods of perfusing and sectioning the hearts and the results obtained are given.

It was found that the glycogen content of the rabbits' hearts varied at different levels; it is highest in the auricles, next highest at the apex, and gradually diminishes toward the base of the ventricles. More glycogen disappears in the first hour of perfusion than at any succeeding time. It was also noted that the ventricles of perfused rabbits' hearts continue to contract after large amounts of ventricular muscle are removed for study. The activity of such hearts apparently is not definitely shortened.

Patek, Arthur, and Weiss, Soma: The Tonus of the Autonomic Nervous System in Arterial Hypertension. New England J. Med. **205:** 330, 1931.

The psychic state and the tonus of the autonomic nervous system of forty-two patients with essential hypertension were compared with that of thirty-seven control patients with a normal cardiovascular system. While no one symptom or sign used for the evaluation of the autonomic nervous system was absolute or pathognomonic, the following symptoms and signs, in combination, distinctively, were more frequently present in patients with essential hypertension than in control subjects: (1) overexcitability, impulsiveness, a tendency to worry; (2) a negative hippus; (3) absence of sinus arrhythmia; (4) negative or reverse oculocardiac reflex; (5) a persistent brittle third tone throughout six sphygmomanometer cuffings; (6) "white" dermographic reaction both to light and to heave pressure; (7) tendency to telangiectasis.

As judged from tests performed, the minute vessels of the skin in arterial hypertension are hyperirritable and have a tendency to react with pressor rather than with depressor responses.

A striking difference in the tonus of the autonomic nervous system in arterial hypertension as compared with that of controls does not exist. On the whole, however, the influence of the parasympathetic nervous system is less and of the sympathetic nervous system more pronounced in patients with arterial hypertension than in control subjects with a normal cardiovascular system.

de Vecchi, Bindo: The Endocarditic Process in Childhood. Arch. Path. **12:** 49, 1931.

The author has analyzed the incidence of valvular endocarditis in children, using the postmortem material of the Institute of Pathological Anatomy of Florence, Italy, amounting to 4,952 autopsies in all. One hundred and seventy-nine cases of endocarditis are noted, ninety-three of which were acute and eighty-three subacute or recurrent. Tables accompanying the text indicate that the incidence of this process is infrequent in the first decade of life, there is a slight increase in the second and a material increase in the third decade in this series, amounting to about forty-three cases. From this point there is a gradual decline to old age.

The author describes the histologic changes occurring in the heart valves. He states that the diagnosis of endocarditis is not always possible with a histological examination and ought to be extended to all cases in which any active participation of valvular tissues can be demonstrated microscopically. This is particularly true in the early period of life. The valvular changes are regarded as the characteristic feature of the process while the thrombotic lesions are considered as merely secondary changes often absent throughout the course of the disease. The histologic changes are described in detail.

It is interesting to note the very infrequent occurrence of this condition in Florence. This infrequency would not coincide with observations in more northern countries, especially in the United States and England. It would be interesting to compare these autopsies with the incidence of heart disease in young children during the first decade of life attending clinics in the same community.

Ellis, Laurence B., and Weiss, Soma: Studies in Complete Heart-Block. 1. The Cardiac Output and the Peripheral Circulatory Mechanism. Am. J. M. Sc. **182:** 195, 1931.

Two studies were made with five patients with complete heart-block; 2 of whom showed no, two moderate and one pronounced functional disability. The two

patients with no functional incapacity and no arteriosclerosis had normal arterial blood pressure, the remaining three had a systolic hypertension. In the absence of cardiac failure, the venous pressure was normal. Four patients had basal metabolic rates in the lower part of the normal range, the fifth had a metabolism 20 per cent below normal. In the four—patients with no circulatory failure at rest normal values for the cardiac output per minute were found. The cardiac output per beat in these patients were increased 40 to 50 per cent about normal. In the fifth patient with circulatory failure in bed, indirect evidence of a decreased blood flow was obtained. The circulating blood volume was reduced in each of four patients; it was not measured in the fifth. The circulation time was estimated by the histamine reaction method. The cardiac output was estimated according to the technic of Field, Bock, Gildea and Lathrop.

The increased stroke volume of the heart, the systolic hypertension, the reduced blood volume and possibly the somewhat lowered basal metabolic rate may be considered compensatory responses tending to maintain a constant and adequate blood supply to the tissues during the prolonged diastolic pause consequent upon the slow heart rate. The degree of elevation of the lactic acid and the changes of blood gases following exercise were normal in one patient who had good functional capacity.

The authors believe that complete heart-block is not incompatible with a normal life and that the prognosis as to health and life is much more dependent on the presence or absence of accompanying myocardial disease than on the block itself.

Cole, Leslie: Heart-Block Following Acute Appendicitis. Lancet, 1: 907, 1931.

Four days following an operation for an attack of acute appendicitis the patient developed irregular pulse which later became slow and which was diagnosed from frequent electrocardiograms as heart-block. No other cause for the disturbance of mechanism could be found. The patient recovered and on the twenty-sixth day the electrocardiogram was quite normal. The most likely explanation is that a mild bacteremia was associated with a subsiding local inflammation in the appendix region and caused a small focal inflammatory lesion in the region of the Bundle of His which interfered temporarily with conduction. Possibly, the pain in the right shoulder and the inflammation in the right conjunctiva may have been due to similar focal lesions.

White, Paul D.: The Treatment of Heart Disease Other Than By Drugs. Jour. Am. Med. Assn., lxxxix, 436.

In the treatment of heart disease the most important relief frequently comes from agents other than drugs. Rest and recreation, physical and mental; exercise, climate, psychotherapy, physical therapy, regulation of the diet, and of the fluid ingested, surgical intervention and venesection all have a place of variable importance in the therapy of acute and chronic heart disease.

The author points out with particular care the relationship that must be maintained between physician and patient. He points out that often times the physician must in his judgment vary his methods to suit the particular circumstances which exist in the individual patient. Ofttimes hard and fast rules cannot be laid down.

Parkinson, John, and Beford, D. Evan: Cardiac Infarction and Coronary Thrombosis. Lancet, 1928, i, 4.

The present paper is based on the clinical study of 100 patients who had experienced one or more prolonged severe attacks of anginal pain and in whom no diagnosis other than myocardial infarction seemed possible. Doubtful cases and those of post-mortem interest only have been excluded. A supplementary study has been made from the records of the Pathological Institute of the London Hospital from 1922 to 1926 for comparison. Altogether 83 such cases are included. The various data concerning cardiac infarction and thrombosis are analyzed in detail. The high incidence of males affected, the suddenness of the onset and the association with sudden death coincide with the figures gained from other similar studies. The authors describe the various usual and special clinical features. They believe that as a rule the electrocardiogram after cardiac infarction is characteristic and occasionally it provides the only objective sign of such a cardiac lesion. The diagnostic feature is the absence of an isoelectric period between the RS- and T-waves, so that a plateau type of curve results in which the R-T interval is either elevated or depressed.

Berman, P., and Mason, V. R.: Coronary Artery Disease and Electrocardiographic Study. Calif. and Western Med., 1928, xxviii, 334.

The authors consider the changes in the electrocardiogram described by Pardee as being specific in the diagnosis of coronary thrombosis. They describe this as a downward sharply peaked T-wave with an upward convexity of the S-T or R-T interval in all or any leads except Lead III. When this type of curve occurs in Lead III with other signs of myocardial damage, it may be of importance. The authors have studied electrocardiograms showing these changes in relation to the clinical course shown by patients in four groups.

Group one includes patients in whom a diagnosis of coronary occlusion made by clinical and electrocardiographic methods was confirmed by post-mortem findings. In an equal period of time there were in the hospital 13 patients who had no electrocardiograms made, but showed occlusion of the coronary artery at autopsy. No clinical diagnosis of the condition had been made in this group.

In a second group, including 18 patients, there were symptons of coronary thrombosis with characteristic electrocardiograms, but in whom there were no autopsies. The electrocardiograms showed other signs of myocardial injury and the patients had clinical signs to coincide with these findings.

Group three includes 9 patients all with syphilitic heart disease. These all showed characteristic coronary T-wave changes.

Group four included 19 patients with characteristic coronary T-wave changes in the electrocardiogram but in whom no clinical diagnosis of occlusion could be made. None of these patients had come to autopsy.

The authors feel that the occurrence of such changes in the electrocardiogram are of value in the diagnosis of coronary thrombosis.

Sprague, Howard B., and White, Paul D.: Auricular Flutter. Jour. Am. Med. Assn., 1928, xc, 1772.

In a man aged forty-nine auricular flutter was diagnosed from the history and by electrocardiogram. The condition had existed apparently for five years

and was unchecked by digitalis or quinidine in full dosage. No cause for the disturbance in mechanism could be found nor was there any evidence of heart disease. The flutter finally stopped abruptly for no known reason. Not infrequently during the course of the flutter, the ventricular rate followed the auricular, without block, at from 240 to 260 beats a minute. At such times palpitation and weakness were distressing.

Book Reviews

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Edited by Doctor Bruno Kisch. Dresden und Leipzig, 1931, Theodore Steinkopff.

These transactions, which record the work of the fourth annual meeting of the German Association for the Study of the Circulation, make up a substantial volume of about 250 pages, which contains some thirty papers and critical reviews dealing with various aspects of cardiovascular disease. About one-half of these are concerned with the chief topic of the meeting—digitalis. Almost every phase of the pharmacology and therapeutics of the digitalis bodies is considered, and one is impressed with the scientific character and high quality of most of the articles. The list of contributors includes a good many well-known names and testifies to the standing of the Association and the quality of its output.

L. A. C.

THE CARDIAC CYCLE by Harrington Sainsbury. New York, 1931, 79 pp., William Wood and Company.

The purpose of this little book, as set forth in the introductory chapter, is to detail the events of the cardiac cycle and to relate them to blood movement and the pulse. The author conveys the impression at the outset, by introducing Newton's laws of motion and emphasizing the application of these principles to cardiodynamics, that he proposes to make the book essentially physical in its point of view.

A discussion of auricular and ventricular systole presents to the reader the notions (1) that the auricle projects its contents into the ventricle and thereby gives rise to a stretching of, and an impact wave in, the ventricle, and (2) that ventricular systole arises in the thin portions of the apex—a fortunate provision of nature to obviate possible disaster through yielding of these weak spots in a forceful contraction. To the isometric phase of the ventricle is assigned the all important rôle of producing the arterial pulse by a kind of impact wave transmitted through the semilunar cusps and over the entire blood column of the arterial tree. This view of the etiology of the pulse can hardly fail to impress most students of cardiac physiology as quite unorthodox but it serves effectively in introducing a discussion of blood pressure in which a more startling view is set forth, namely, that diastolic pressure as usually determined is a misnomer. At this juncture an old and somewhat overlooked part in cardiac anatomy is brought into a major rôle. The bulbus aortae, we are told, forms a kind of elastic compensating chamber that exerts a continuous (systolic) pressure for the blood movement.

The final chapter of the book relates mainly to the mechanism of lymph flow. A discussion is given of the physicochemical and other factors, but the emphasis is given to the part played by the pulse as a propulsive force that drives the lymph.

The format of the book is good, the style is generally clear and agreeable, and the mistakes are few, but the substance of the arguments fails to carry conviction. Modern methods of recording, with sensitive instruments, simultaneously

the changes in intraventricular pressure and the pulsations in a central and peripheral artery present stronger evidence concerning the etiology of the pulse than is obtained from arguments about the physical attributes of the events in a cardiac cycle. Similarly, experimental results on the intraarterial pressure and blood velocity leave no room for doubt as to the fact of a diastolic pressure in the sense that the term is usually applied.

D. J. E.